FORMULATION AND EVALUATION OF ATORVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS USING SUPER DISINTEGRANTS

Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University

Chennai - 600032

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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APRIL 2013

DECLARATION BY THE CANDIDATE

I hereby declare that the dissertation entitled **"FORMULATION AND EVALUATION OF ATORVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS USING SUPER DISINTEGRANTS''** is a bonafide and genuine research work carried out by me under the supervision of **Mrs V Prathiba, M.Pharm.,** Asst.Professor, Department of Pharmaceutics, K.K.College of Pharmacy, Chennai, during the year 2012-2013. And I also declare that the same has not performed as the basis for the award of any Degree, Diploma, Associateship, or Fellowship of any other University or Institution. This dissertation submitted in partial fulfillment for the award of the **Degree of Master of Pharmacy (Pharmaceutics)** to The Tamil Nadu Dr. M.G.R Medical University, Chennai – 600032.

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ACKNOWLEDGEMENT

I highly indebted to **Mr.K.R. Arumugam,** M.Pharm., Chairman, KK College Pharmacy, Chennai for his help support care and encouragement.

I take this opportunity to express my profound gratitude and deep regards to my guide **Mrs.V.Pratibha,** M.Pharm., for her exemplary guidance, monitoring and constant encouragement throughout the course of this thesis. The blessing, help and guidance given by him time to time shall carry me a long way in the journey of life on which I am about to embark.

I also take this opportunity to express a deep sense of gratitude to **Srinivas Reddy**, Director of RPTL, Hyderabad for his cordial support, valuable information and guidance, which helped me in completing this task through various stages.

I extend my sincere thanks **Dr.V.Vaidhyalingam**, M.Pharm., PhD., Director of K.K.College of Pharmacy for his valuable suggestions, encouragement and support to do the work efficiently.

I take pride to thank **Prof.A.Meena**, M.Pharm. (PhD)., Principal of K.K.College of Pharmacy for the continuous source of encouragement, inspiration and constructive suggestions and her immense support for the successful completion of my project work.

I wish to express my heartily felt gratitude to the management of **RPTL labs** for their co-operation & encouragement during my project work.

I wish to extent my sincere thanks to **Mrs.Usha**, Librarian and all the **Teaching** and **Non-teaching staff members** of K.K.College of pharmacy and also the **Lab Technicians** and **Attenders** for their help and support to make this work successful.

I heartfully thank my friends **V. V. Ramu, Siva Reddy** and **S. K. Mobeen** for helping in completing my project.

I sincerely thank my classmate **Mr.RNBS Naresh Chandra**, **Ms.Farha younus Mr.Vinil Kumar, Pavan Kumar R** and **Murali Krishna Reddy** for being wonderful team members who were always there for me and encouraged me at every step. Also I

heartfully thank to each and every present M Pharm(Pharmaceutics) juniors for their timely help during the making of this book.

I am indebted to my father **S. Balaguravaiah** and also my mother **S. Malakondamma** who are the foundation stone of the platform where I am standing today. My work is the result of prayers and blessing of my mother and hard work of my father enabling me to reach this point of my career. It is because of them I have reached this position. Also I thank my dear brother and sister who helped me and encouraged all throughout the project.

Finally I am very thankful to the Almighty God for bestowing me with good knowledge, health, happiness and giving me strength for completing this project work.

THIS WORK IS DEDICATED TO MY PARENTS, LECTURERS & FRIENDS

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LIST OF ABBREVIATIONS

Sl. no.	Abbreviation	Full form
1.	A^0	Angstrom
2.	Abs	Absorbance
3.	ACE	Angiotensin converting enzyme
4.	Avg	Average
5.	API	Active Pharmaceutical Ingredient
6.	AT	Angiotensin
7.	ARB	Angiotensin receptor blocker
8.	AUC	Area under curve
9.	BCS	Bio-pharmaceutical classification system
10.	BP	British Pharmacopoeia
11.	Cm	Centimetre
12.	Cps	Centipoise
13.	CR	Controlled release
14.	ER	Extended release
15.	et.al.	and others
16.	FTIR	Fourier Transform Infra-red Spectrophotometer
17.	G	Gram(s)
18.	g/mol	Gram/mole
19.	g/cc	Gram/cubic centimeter
20.	G.I.T	Gastrointestinal Tract
21.	Hr	Hour(s)
22.	HPMC	Hydroxypropyl methylcellulose
23.	IP	Indian Pharmacopoeia
24.	IR	Infra red
25.	JP	Japanese Pharmacopoeia

26.	KPa	Kilo Pascal
27.	log P	Partition coefficient
28.	mcg/µg	Microgram(s)
29.	Mg	Milligram(s)
30.	min(s)	Minutes
31.	mL	Millilitre(s)
32.	mPa	milli pascal
33.	NaOH	Sodium hydroxide
34.	Nm	Nanometer
35.	^{o}C	Degree centigrade
36.	Ppm	Parts per million
37.	q.s.	Quantity sufficient
38.	Rpm	Revolutions per minute
39.	SD	Standard deviation
40.	SR	Sustained release
41.	TDT	Tablet dissolution tester
42.	USP	United States Pharmacopoeia
43.	%	Percentage
44.	% w/v	Percentage weight/volume
45.	% w/w	Percentage weight/weight
46.	SSG	Sodium starch glycolate
47.	MCC	Micro crystalline cellulose
48.	CCS	Croscarmellose sodium
49.	API	Active pharmaceutical ingredient
50.	LDL	Low density lipoprotein
51.	ICH	International conference on harmonization

1 INTRODUCTION

Tablet is a solid pharmaceutical dosage form containing drug substances with or without suitable diluents and prepared by compression or molding method. Drug delivery system (DDS) is a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Solid oral delivery systems are less expensive to manufacture**,** Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. They do not require sterile conditions. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics.

Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance.

Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

The importance of many drug delivery system is to offers a therapeutic amount of drug in the particular site in the body to reach promptly and then to maintain the desired drug concentration. i.e., the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.1 Oral drug delivery [1, 2]:

Oral drug delivery is the most widely used route of administration among all the routes that have been explored for systemic drug delivery through pharmaceutical products of various dosage forms. Oral route is considered most natural, easy to administer, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective process.

For the past centuries, there has been increased demand for patient complaint dosage forms. As per result the demand for the technologies has been raised 3 fold annually. Since the development cost of new chemical entity is very expensive, the pharmaceutical industries are concentrating on the discovering of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects and to release the active drug immediately after oral administration to get rapid and complete systemic drug absorption. Such IR products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentration rejects according to the drugs pharmacokinetic profiles, conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to perform maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effect.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects and oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are most popular because it is ease of administration, accurate dosage form, self-medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important disadvantage of these dosage forms is the difficulty to swallow

Oral dosage form is the most widely used route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively less expensive of manufacture, package.

1.2. IMMEDIATE RELEASE DRUG DELIVERY SYSTEM [3:]

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

- Tablet must be sufficiently strong and resistant to shock, abrasion,
- Organoleptic properties are improved by coating of tablet (taste, appearance and odour).
- Tablet should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- It should be uniform in weight and in drug content of the individual tablet. It is measured by the weight variation and content uniformity tests.
- Drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration.
- Tablets must be elegant in appearance, characteristic shape, color and other markings necessary to identify the product. Tablets must retain all these functional properties which include drug stability and efficacy.
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in large amount and emergency supplies can be carried by patients.
- Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable etc.
- In comparison to parenterals dosage form, a doctor or a nurse is not required for administration.i.e, Self-administration is possible.

Advantages of immediate release drug delivery systems[4] :

- It releases the drug immediately.
- More flexibility for adjusting the doses.
- It can be prepared with minimum dose of drugs.
- There were no dose dumping problems.
- Immediate release drug delivery systems can be used in both initial stage and Final stage of disease.
- At the particular site of action the drug is released from the system.

Disadvantages:

- It is too difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability and slow dissolution into a tablet.
- It is very slow onset of action as compared to parenterals, liquid orals and capsules.
- The amount of liquid drug (e.g., vitamin E, simethicone) that can be trapped into a tablet is very less amount.
- Difficult to swallow for children, terminally ill and geriatric patients.
- Patients undergoing radiotherapy cannot swallow tablet.

TABLETS

"In 1843, the first patent for a hand operated device used to form a tablet was granted." Tablets may be defined as a solid preparations in which containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredient "liberated". For the systemic drug delivery tablets are mainly used but also for local drug action. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].

Tablets may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They

may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated or non-coated

Properties of tablets:

- It should have sufficient strength and resistance to shock and abrasion to with stand handling, manufacturing, packing, shipping and use.
- Tablets must be uniform in weight and in drug content of each tablet.
- Tablets must be elegant in appearance and must have characteristic shape, colour and other markings necessary to identify the product.
- Tablet drug content of tablet must be bioavailable.
- Tablets must retain all these functional attributes, which include drug stability and efficacy.

Advantages of Tablets:

- Tablets unit dosage form, and they offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Tablets are the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- Tablet are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with least tendency for "hang-up" above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamperproof dosage form".

Disadvantages of tablets:

- In some drugs resist compression into dense compacts, owing to their amorphous nature/ flocculent/ low density character.
- Drugs are with poor wetting, slow dissolution properties, optimum absorption high in GIT or combination of these features may be difficult or impossible to formulate.
- Bitter tasting drugs, drugs with objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or a special type of coating which may increase the weight of the finished products.
- Tablet onset of action is slow when compared with parenterals, liquid orals and capsules.
- It is difficult to convert a high dose poorly compressible API in to a tablet of suitable size for human use. (Lachman L et al., 1990)

1.3. TYPES OF TABLETS

Tablets are classified as follows:

a) According to the drug release rate from the tablet
b) According to the method of manufacturing
c) According to the route of administration or function

According to The Drug Release Rate From The Tablet (USP classification)[4]:

1) **Immediate release (conventional) tablets**:

The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as solution. It is the most common type and includes:

- Disintegrating tablet- e.g. Acetaminophen tablet
- Chewable tablet - e,g. Antacid tablet
- Sublingual tablet - e.g. Vicks menthol tablet
- Buccal tablet - e.g. Vitamin-c tablet
- Effervescent tablet - e.g. Dispirin tablet (Asprin)

a) Disintegrating tablets:

An orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited amount of over-the-counter (OTC and prescription

medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole.

The ODT serves as an alternative dosage form for patients who experience dysphagia (difficulty in swallowing) or for where compliance is a known issue and therefore an easier dosage form to take ensures that medication is taken.

Common for all age groups, dysphagia is observed in about 36% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities during the last decade, ODTs have become available in a variety of therapeutic markets, both OTC and by prescription. Additional reason to use an ODTs is the convenience of a tablet that can be taken without water.

b) Chewable tablets:

Sublingual and buccal medications are administered by placing them in the mouth, either under the tongue (sublingual) or between the gum and the cheek (buccal). The medications dissolve rapidly and are absorbed through the mucous membranes of the mouth where they enter into the bloodstream. The medications are compounded in the form of small quick-dissolving tablets, sprays, lozenges or liquid suspensions.

c) Buccal tablets:

Sublingual and buccal medications are given for a variety of conditions. The most common sublingual medication is the nitroglycerin tablet. Its rapid action to relax the blood vessels reduces the workload on the heart and relieves the pain of angina pectoris. Other buccal and sublingual medications however, serve a variety of purposes-such as narcotic pain relief, migraine pain relief, blood pressure control, and mental decline due to dementia (i.e., ergoloid) mesylates). This form of medication is extremely effective, because it bypasses the digestive system and is absorbed into the bloodstream in minutes.

Not all medications can be prepared for sublingual or buccal administration; some of the compounding difficulties are taste, solubility, and dosage limitations of the medicine.

d) Effervescent tablets:

Effervescent or carbon tablets are tablets which are designed to break in contact with water or another liquid, releasing carbon dioxide in the process. Rapid breakdown often may cause the tablet to dissolve into a solution and is also often followed by froth. These kinds of tablets are usually used to deliver drugs or to encapsulate cleaning products such as the enzymatic cleaners designed for wetsuits.

These tablets are products of compression of component ingredients into a dense mass, which is packaged in an airtight container or a blister pack. When necessary, people is can drop them into water or another liquid to make a solution

2) Modified – release tablets: They have release features based on time, course or location. They must be swallowed intact.

- Extended – release tablet**:** allowing the reduction in dosing frequency
- Delayed - release tablet**:** drug release is delayed due to physiological conditions

E.g.: Enteric coated tablets- the drug is released in the upper part of small intestine after which the preparation will pass the stomach. If the drug is sensitive to acid or irritant to the stomach lining, an enteric coating can be used.

According to the Method of Manufacturing

(a) Compressed tablet- e.g. Paracetamol tablet

(b) Molded tablet- e.g. Nitroglycerin Tablets

According to Their Route of Administration or Function[5]:

1) Tablets ingested orally

These tablets are meant or be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 99% of the tablets manufactured today are ingested orally.

- Compressed tablets - e.g. Paracetamol tablet
- Multiple compressed tablets - e.g. Antacid tablet
- Multilayered tablets - e.g. Ephedrine hydrochloride tablet
- Sustained action tablets - e.g. Verapamil HCl tablet
- Enteric coated tablets - e.g. Asprin tablet
- Sugar coated tablets - e.g. Multi vitamin tablet
- Film coated table - e.g. Metronidazole tablet
- Chewable tablets - e.g. Antacid tablet.

2) **Targeted tablet**

1. Floating tablet- e.g. Theophylline tablet
2. Colon targeting tablet- e.g. Indomethacin tablet

3) **Tablets used in the oral cavity**

The tablets under this group are aimed to release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

a) Buccal tablets- e.g. Vitamin-c tablet

b) Sublingual tablets- e.g. Vicks menthol tablet

c) Lozenge tablets and trouches- e.g. Clotrimazole tablet

d)Dental cones

4) Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

- Implantation tablets, e.g. Adrenaline
- Vaginal tablets, e.g. Clotrimazole tablet

5) Tablets used to prepare solutions

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

Effervescent tablets, e.g. Dispirin tablet (Asprin)

6) Molded tablets or tablet triturates

a) Dispersing tablets,- e.g. Enzyme tablet (Digiplex)

b) Hypodermic tablet-, e.g. Morphine Tablet

Disintegrants are an essential component to tablet formulations. While rapidly disintegrating tablets do not necessarily ensure fast bioavailability, slowly disintegrating tablets almost always assure slow bioavailability

MECHANISM OF TABLET DISINTEGRATION[6, 7 :]

The mechanism by which the tablets are broken into small pieces and then produce a homogeneous suspension is based on the following steps:

- Capillary action/ water wicking
- By swelling
- Air expansion /heat of wetting
- Due to disintegrating particle/particle repulsive forces
- Due to deformation
- Due to release of gases
- By enzymatic reaction

- Disintegrants are an essential component to tablet formulations. While rapidly disintegrating tablets do not necessarily ensure fast bioavailability, slowly disintegrating tablets almost always assure slow bioavailability

INGREDIENTS TO BE USED FOR ORALLY DISNTEGRATING TABLETS

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Excipients balance the properties of the actives in FDDTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipients should be preferably around 30–35^{0}C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast- dissolving formulation for achieving the desired sensory and melting characteristics, and for the

faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used.

1.6. SUPER DISINTEGRANTS IN IMMEDIATE RELEASE TABLETS[8-11]:

A disintegrant is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation. It can also be used with products that are wet granulated. While there are some tablets fillers (starch, MCC) which aid in disintegration. There are more effective agents referred to as super disintegrants.

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

ADVANTAGES:

1. Effective in lower concentrations.
2. Less effect on compressibility and flowability.
3. More effective intragranularly.

Commonly used superdisintegrants are:

- **Sodium Starch Glycolate (Explotab, primogel)** used in concentration of 2-8 % & optimum is 4%.

Mechanism of Action: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium:

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation.

TABLE 1:Super disintegrants used in immediate release formulations

Super disintegrants	Example	Mechanism of action	Special comment
Crosscarmellose	Cross linked Cellulose	- Swelling and wicking both Swells very little.	- Swells in two dimensions. - Direct compression or granulation.
Sodium starch glycolate	Cross linked Starch	- Swells 7-12 folds in < 30 seconds.	- Swells in three dimensions and high level serve as sustain release matrix.

- **Gas producing disintegrants**

  Gas producing disintegrants are used in extra rapid disintegration or readily soluble formulation is required. It have also been found the value when poor disintegration characteristics have resisted for other methods of improvement. Care should be taken during tabletting particularly on moisture level.

  In many instances lower concentration can be used with gas producing disintegrants than required by other disintegrating agents. Certain peroxides that release oxygen have been tried but they do not perform as well as those releasing carbon dioxide.

1.7. TABLET-MANUFACTURING METHODS

1). Direct compression

2). Granulation

DIRECT COMPRESSION [12]:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and for suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

Manufacturing steps for direct compression

Following are the steps involved in the manufacturing of direct compression:

- Milling of drug and excipients
- Mixing of drug and excipients
- Tablet compression

GRANULATION

Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates.

Granulation method can be broadly classified into two types:

(a) Wet granulation

(b) Dry granulation

a) Wet Granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying

Important steps involved in the wet granulation

- Mixing of the drug(s) and excipients
- Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass
- Coarse screening of wet mass using a suitable sieve

- Drying of moist granules
- Screening of dry granules through a suitable sieve
- Mixing of screened granules with disintegrant, glidant, and lubricant

Limitations of wet granulation:

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements. Loss of material during various stages of processing.
- Stability may be a major concern for moisture sensitive or thermolabile drugs.
- Multiple processing steps give complexity and make validation and control difficult.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

b) Dry Granulation [12]:

In dry granulation process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. There are two methods for dry granulation. The more widely used method is slugging, where the powder is compressed and the resulting tablets or slugs are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilsonator.

Steps in dry granulation

- Milling of drugs and excipients
- Mixing of milled powders
- Compression into large, hard tablets to make slugs
- Screening of slugs
- Mixing with lubricant and disintegrating agent
- Tablet compression

Two main dry granulation processes

a) **Slugging process:** Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b) **Roller compaction:** The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs the aggregates are screened or milled for production into granules. (Parikh, Handbook of pharmaceutical granulation technology).

Manufacturing defects in tablets:

Problems involved during the manufacturing of tablets include:

- Capping
- Lamination
- Chipping
- Sticking
- Picking
- Mottling
- Hardness variation
- Double impression

1.8 Excipients used in tablet formulation:

Excipients means any component other then the active pharmaceutical ingredients intensionaly added to the formulation of a dosage form. There are many guidelines exist to aid in the selection of non toxic excipients such as IIG (inactive ingredient guide). GRAS (generally regarded as safe). While selecting excipients for any formulation following things should be considered wherever possible.

Keep the minimum number of excipients, and minimize the quantity of each excipients and multifunctional excipients may be given by preference over single functional excipients will plays acrucial role in drug delivery system, determining its quality and performance. Excipients are normally nontoxic – eg: excipients induced toxicities which includes renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested like mannitol, hypersensivity reaction from lanolin and cardiotoxicity induced by propylene glycol.

Super disintegrants :

Ex:- sodium starch glycolate, croscarmelose, crospovidone.

Diluents:-

Ex:- Lactose monohydrate, micro crystalline cellulose,

Glidents:-

Ex:- Magnesium stearate, colloidalsillicon dioxide, starch and talc.

DISEASE PROFILE

Hyperlipidemia: [32, 33, 34]

Hyperlipidemia is one of the greatest risk factors contributing to prevalence and severity of cardiovascular diseases. The term Hyperlipidemia means high Lipid levels (lipoprotein) or high Cholesterol levels in the blood. It is a condition where there will be elevations in the levels of plasma total and LDL(Low density lipoprotein) with variable changes in HDL(High density lipoprotein).This causes Cardiovascular diseases such as atherosclerosis and atherosclerosis associated conditions like Coronary heart disease(CHD),Ischemic cerebrovascular disease and Peripheral vascular disease which is currently the leading cause of death and illness in developed countries and will soon become the pre-eminent health problem worldwide.Dyslipidemias including Hyperlipidemia (Hypercholesterolemia)and low levels of High density lipoprotein cholesterol(HDL-C) are major causes of increased atherogenesis,both genetic disorders and lifestyle(Sedentary behavior and diets high in calories, saturated fat and cholesterol)contribute to the dyslipidemias seen in developed countries. The epidemiologic data shows that the prevalence of dyslipidemia in Indian adult's aged 31-40 age groups is more than in ≤30age group. High density lipoprotein cholesterol (HDL-C) was abnormally low in 64.2% males and 33.8% in females. Thus, prevalence of dyslipidemia was observed to be higher in males than in females in India.

Atherosclerosis, a progressive disease characterized by the accumulation of cholesterol, low density lipoprotein-cholesterol (LDL-C) and fibrous elements in the large arteries. Arteries are normally smooth and unobstructed on the inside, as the person ages a sticky substance called plaque forms in the walls of your arteries. Plaque is made of lipids and other materials circulating in the blood. As more plaque builds up, arteries narrow stiffen and plaque rupture occurs and thus enough plaque may build up to reduce blood flow through arteries. Plaque rupture leads to platelet activation and thrombosis which leads to blood clots. This increases the risk of heart disease, stroke and other vascular diseases. Thus atherosclerosis constitutes the single most important contributor to this growing burden of cardiovascular disease. World health organization (WHO) reports that high blood cholesterol contributes to approximately 56% of cases of cardiovascular diseases worldwide and causes about 4.4million deaths each year.

Lipoproteins:

Lipids (fat-soluble molecules) are transported in a protein capsule. The size of that capsule determines its density. Lipoproteins are macromolecular assemblies that contain proteins and lipids, including free and esterified cholesterol, triglycerides, and phospholipids. The protein components known as apolipoproteins, provide structural stability to the lipoproteins, and also may function as ligands in lipoprotein–receptor interactions or as cofactors in enzymatic processes that regulate lipoprotein metabolism. In all lipoproteins, the most water-insoluble lipids (cholesteryl esters and triglycerides) are core components, and the more polar water-soluble components (apoproteins, phospholipids and unesterified cholesterol) are located on the surface. The lipoproteins have been divided into classes on the basis of their particle size and density. They also differ in the nature of apoproteins, the ratio of TG and CHE, tissue of origin and fate.

Classification:

The major class of lipoproteins and their properties are presented and describes apoproteins that have well-defined roles in plasma lipoprotein metabolism. Five major lipoproteins exist, each with a different function:

- Chylomicrons
- Very–low-density lipoproteins (VLDLs)
- Intermediate-density lipoproteins (IDLs)
- Low density lipoproteins(LDLs) and
- High density lipoproteins(HDLs)

The protein components of the lipoprotein are known as apolipoproteins or apoproteins. The different apolipoproteins serve as cofactors for enzymes, and ligands for receptors.

Pathways of Lipid Metabolism:

Each class of lipoprotein has a specific role in lipid transport. Three main pathways are responsible for the generation and transport of lipids within the body:

- Exogenous pathway

- Endogenous pathway

Exogenous pathway:

- Cholesterol and triglycerides(CHO + TG) are absorbed from the GIT are transported in the lymph and than in the plasma as Chylomicrons to capillaries in muscle and adipose tissues. Here the core triglycerides are hydrolysed by lipoprotein lipase, and the tissues take up the resulting free fatty acids.
- Cholesterol is liberated within the liver cells and may be stored, oxidised to bile acids or secreted in the bile unaltered. Alternatively it may enter the endogenous pathway of lipid transport in VLDL.

Endogenous pathway:

- Cholesterol and newly synthetised Triglycerides(TG‘s) are transported from the liver as Very low density lipoprotein(VLDL) to muscle and adipose tissue, there TG are hydrolysed and the resulting fatty acids enter the tissues
- The lipoprotein particles become smaller and ultimetaly become LDL , which provides the source of CHO for incorporation into cell membranes, for synthesis of steroids, and bile acids. Cells take up LDL by endocytosis via LDL receptors that recognise LDL apolipoproteins .
- Cholesterol can return to plasma from the tissues in HDL particles and the resulting cholesteryl esters are subsequently transferred to VLDL or LDL
- One particular subtype of LDL is associated with atherosclerosis (localised in atherosclerotic lesions). LDL can also activate platelets, constituting a further thrombogenic effect.

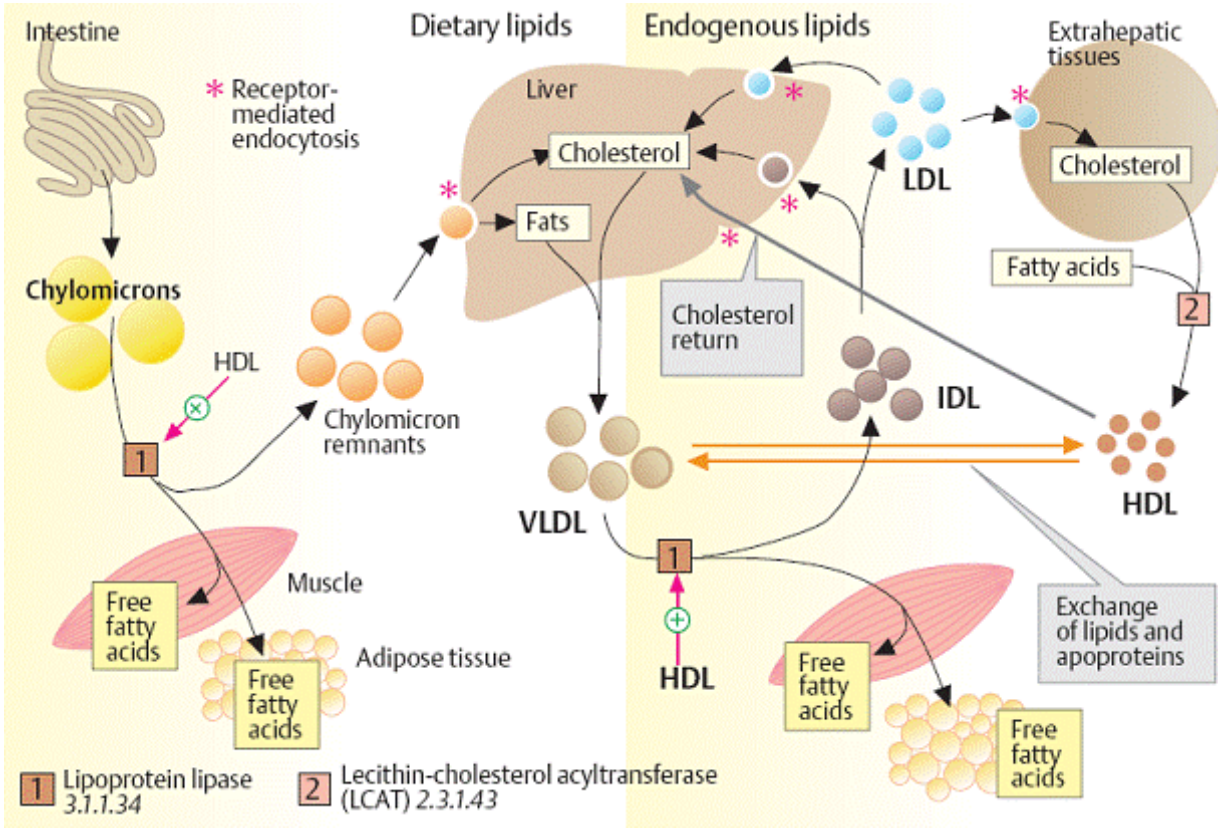


FIG: 1 LIPOPROTEIN METABOLISM

Causes:

Hyperlipidemia also known as hyperlipoproteinemia or hyperlipidaemia (British English) is divided into two sub-types. They are:

- **Primary** hyperlipidemia is usually due to genetic causes (such as a mutation in a receptor protein)
- **Secondary** hyperlipidemia arises due to other underlying causes such as diabetes.

The most common causes of acquired hyperlipidemia are:

- ❖ Diabetes mellitus
- ❖ Use of drugs such as diuretics, beta blockers, and estrogens

Other conditions leading to acquired hyperlipidemia include:

- ❖ Hypothyroidism
- ❖ Renal failure
- ❖ Nephrotic syndrome
- ❖ Alcohol usage
- ❖ Some rare endocrine disorders and metabolic disorders

Treatment:

Many drugs have come in market as anti-hyperlipidemic drugs also known as hypolipidemic drugs. Diverse group of pharmaceuticals are used in the treatment of hyperlipidemias. They are called lipid-lowering drugs (LLD) or agents. These are the drugs which lower the levels of lipids and lipoproteins in blood.

The main agents used clinically as hypolipidaemic drugs are:

- HMG-CoA reductase inhibitors(Statins)
- Bile acid sequestrants(Resins)
- Fibric acid derivatives
- Nicotinic acid(Niacin)
- Other Hypolipidaemics.

Antihyperlipidemic drugs decrease cholesterol and triglyceride levels in several ways. Although the end result is a lower lipid blood level, each has a slightly different action.

Atorvastatin calcium:

Atrovostatin is drug which is classified under HMG-CoA reductase inhibitors also called as statins. This drug appears to have one of two activities, namely

- Inhibiting the manufacture of cholesterol or
- Promoting the breakdown of cholesterol. Different statins differ in their potency and maximal efficacy in reducing LDL-CH levels.

2 REVIEW OF LITERATURE

Patel Dipika, et al (2012)[16] Formulation, development and evaluation of immediate release tablets containing atorvastatin calcium drug was studied by Patel Dipika, Patel Vijayakumar[16] to develop amorphous form of Atorvastatin Calcium into immediate release tablets. Pre-formulation studies and drug excipients compatibility studies was done initially and the results obtained were directs the way and method of formulation. Preformulation and drug excipient compatibility study, prototype formulation carried out for the highest dose of Atorvastatin (80 mg) and optimized to get the final formula. All the mentioned batches were done by wet granulation method. Granules were evaluated for tests such as loss on drying (LOD), preformulation studies such as bulk density, tapped density, compressibility index and Hauser's ratio and sieve analysis before compression. Tablets were tested for weight variation, thickness, hardness, friability and dissolution. In vitro dissolution studies were performed and *f1* and*f2* values were calculated. Dissolution profile of F8 was matched perfectly with marketed (innovator) formulation and *f2* value was found to be excellent. Also the impurity profile and stability result of F8 was found to be excellent. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

Sachin v. Wankhede, et al (2012)[17] Formulation and stabilization of atorvastatin tablets by Sachin v. Wankhede, S.Y.Manjunath, Subal Debnath' was planned to develop Atorvastatin calcium amorphous into immediate release tablets.Pre-formulation study and drug excipients compatibility study was done initially and the results obtained were directs the way and method of formulation. Preformulation and drug excipient compatibility study,prototype formulation carried out for the highest dose of Atorvastatin calcium (80 mg) and optimized to get the final formula. Atorvastatin calcium (amorphous) is highly susceptible to hydrolysis and oxidation. So wet granulation method was avoided. All the mentioned batches were done by dry granulation method by roller compaction. Granules were evaluated for tests such as loss on drying (LOD), preformulation studies such as bulk density, tapped density, compressibility index and Hauser's ratio and sieve analysis before compression. weight variation of the tablet were tested, thickness, hardness, friability and dissolution. In vitro dissolution studies were performed and Formulation 1 (F1) and Formulation 2 (F2) values were calculated. Dissolution profile ofF5 was matched perfectly with marketed (innovator) formulation and F2 value was found to be excellent, also the impurity profile and stability result of F5

was found to be excellent. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

Subhadeep Chowdhury, Subhabrotamajumdar et al (2010)[18] Statistical optimization of fixed dose combination of Glimepiride and Atorvastatin calcium in immediate release tablet formulation was studied and long term administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatmentwith diet alone or diet with insulin. For this complication atorvastatincalcium can be used to reduce the cardiovascular mortility. The objective of the present study was to evaluate the effects of two factors (amount of carboxymethylcellulose sodium and sodium starch glycolate) on drug release of atorvastatin calcium and glimepiride from the tablet in order to optimize the formulation by 2 factor 3 level factorial design. Twoindependent variables taken were carboxymethylcellulose sodium (10mg, 12.5mg and 15 mg)and sodium starch glycolate (2.5 mg, 5mg and 7.5mg). The evaluated response were percentage release of atorvastatin calcium in 60 min (Y1) and percentage release of glimepiride in 60 min (Y2) was taken as the response variables.Drug release was measured in USP 2 (paddle type) apparatus using 900 ml 0.05 M phosphate buffer(pH6.8) solution at a rotation speed 75 rpm. The dissolution data revealed that amount of carboxymethylcellulose sodium and sodium starch glycolate are very important to achieve optimum formulation. Using responses and resulted statistical equations, optimum formulation was predicted. It shows that sodium starch glycolate has more effect than carboxymethylcellulose sodium on the tablet formulation and formulation with 14.78 mg of carboxymethylcellulose sodium and 7.5 mg of sodium starch glycolate is the optimized formulation. The optimized formulation produced dissolution profiles that were closed to predicted values.

M.Manikandan, K Kannan, Sthirumurugu, R.Manavalan et al[19]Design and evaluation of amlodipine besilate and atorvastatin calcium tablets was studied by M.Manikandan, K Kannan, Sthirumurugu, R.Manavalan. Amlodipine besilate is a calcium channel blockers used for the treating high blood pressure, certain types of angina and coronary heart failure. Atorvastatin calcium known as Statins is used for lowering blood cholesterol and in the treatment of primary hypercholesterolemia and dyslipidemia. The objective of the present investigation was to formulate and evaluate an oral administrable tablet containing Amlodipine besilate and Atorvastatin calcium by wet granulation method. The tablets were prepared using Microcrystalline cellulose, Calcium

carbonate, polysorbate 80, Hydroxypropyl cellulose, Pregelatinized starch, Croscarmellose sodium, Colloidal anhydrous silica and Magnesium stearate. Preformulation studies were performed prior to compression. The prepared tablets were evaluated for various pre-compression characteristics like angle of repose, bulk density, tapped density, cars index and hausner's ratio, loss on drying and post-compression characteristics like Appearance, Weight variation, Hardness, Thickness, Disintegration, Friability, In vitro Dissolution studies. The stability studies were carried out for the optimized batch for three months and it showed no significant changes in the physicochemical parameters and in vitro release pattern. The present study concludes that combined pill has the potential to improve the management of hypertensive patients with additional cardiovascular risk factors, especially dyslipidemia by reducing pill burden and prescription costs

V.Mallikarjun, P.Rajasridharrao et al[20] Formulation and evaluation of bilayer tablets of atorvastatin and nicotinic acid in different media by was aimed to formulate and evaluate the bilayer tablets using different media, toknow the release studies in which media the release of the drug is in controlled manner. The bilayer tablets of Atorvastatin (AT) calcium and Nicotinic acid (NA) were prepared to give Atorvastatin asimmediate release and controlled release of Nicotinic acid. Bi-Layer tablets consists of two layers i.e.,immediate release layer containing of disintegrants like croscarmellose sodium and Cross-Povidone and controlled release layer containing HPMCK100M as retard layer. Combination of Atorvastatin andnicotinic acid is accepted to bring down cholesterol levels. Three different formulations were prepared bywet granulation method which consists of various disintegrants and polymer in different ratios namelyATNA1, ATNA2 and ATNA3.The tablets were evaluated for various parameters like weight variation, thickness, hardness andfriability. The release studies were carried out using different media i.e. buffer PH 7.4, 6.8, 4.5 and 0.1N HCl using USP dissolution testing apparatus II (paddle type) for 12hrs.The controlled release layer of Nicotinic acid formulation containing HPMC K100 shows optimized drug in 0.1N HCl within 12 hours.Thelayer of atorvastatin containing Cross-Povidone shown satisfactory release from dosage forms.Hence, from the above study we conclude that ATNA2 has shown good release in 0.1N HCl compared to other media with different ratios of polymers.

S.Brito raj et al (2011)[21] Inlay tablet of atorvastatin calcium with sustained release metoprolol tartarate was designed a dual retard technique of once daily Inlay tablet of Atorvastatin calcium as Immediate Release (IR) formulation with Matrix tablet of

Metoprololtartarate as Sustained release (SR) formulation for Hypertension and Atherosclerosis. The Inlay tablet was prepared by Wet granulation method. The Compatibility of the drug with various excipients was studied by Differential scanning calorimetry (DSC). The formulations were developed by using polymers like Guar gum, Eudragit, HPMC for sustained release layer and Sodium starch glycolate, Cross povidone, Cross carmellose sodium as Super disintegrants for immediate release layer. Six formulations (F1-F6) were prepared and evaluated for various parameters like Thickness, Hardness, Weight variation, Disintegration, Swelling Erosion behavior, Simultaneous analysis by both UV and HPLC, In vitro release and Stability studies at 40º±2ºC, RH 70±5%. Among the six formulations (F1-F6), F4 possess expected release pattern in both immediate release layer and sustained release layer. Further from the Release kinetics it was revealed that the drug release for formulation F4 follows Zero order. Thus the study concludes that the formulation can overcome the disadvantages of other multilayered tablets and can be used to treat the patients having high blood pressure with Hyperlipidemia that plays major risk factors for CHD.

Min-soo kim et al(2008)[22] Preparation, characterization and in vivo evaluation of amorphous atorvastatin calcium nanoparticles using supercritical anti solvent (sas) process by Min-soo kim was studied to deal with amorphous atorvastatin calcium nanoparticles were successfully prepared using the supercritical antisolvent (SAS) process. The effect of process variables on particle size and distribution of atorvastatin calcium during particle formation was investigated.Solid state characterization, solubility, intrinsic dissolution, powder dissolution studies and pharmacokinetic study in rats were performed. Spherical particles with mean particle size ranging between 152 and 863 nm were obtained by varying process parameters suchas precipitation vessel pressure and temperature, drug solution concentration and feed rate ratio of CO2/drug solution. XRD, TGA,FT-IR, FT-Raman, NMR and HPLC analysis indicated that atorvastatin calcium existed as anhydrous amorphous form and no degradation occurred after SAS process. When compared with crystalline form (unprocessed drug), amorphous atorvastatin calcium nanoparticles were of better performance in solubility and intrinsic dissolution rate, resulting in higher solubility and faster dissolution rate. Inaddition, intrinsic dissolution rate showed a good correlation with the solubility. The dissolution rates of amorphous atorvastatincalcium nanoparticles were highly increased in comparison with unprocessed drug by the enhancement of intrinsic dissolution rateand the reduction of

particle size resulting in an increased specific surface area. The absorption of atorvastatin calcium after oral administration of amorphous atorvastatin calcium nanoparticles to rats was markedly increased.

Ankushchoudhary et al (2012)[23] Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability was done by ankushchoudhary to deal with Atorvastatin has low aqueous solubility resulting in low oral bioavailability (12%) and thus presents a challenge in formulating a suitable dosage form. To improve the aqueous solubility, a solid dispersion formulation of atorvastatin was prepared by lyophilization utilizing skimmed milk as a carrier. Six different formulations were prepared with varying ratios of drug and carrier and the corresponding physical mixtures were also prepared. The formation of a solid dispersion formulation was confirmed by differential scanning calorimetry and X-ray diffraction studies. The optimum drugto-carrier ratio of 1:9 enhanced solubility nearly 33-fold as compared to pure drug. In vitro drug release studies exhibited a cumulative release of 83.69% as compared to 22.7% for the pure drug. Additionally, scanning electron microscopy studies suggested the conversion of crystalline atorvastatin to an amorphous form. In a Triton-induced hyperlipidemia model, a 3-fold increase in the lipid lowering potential was obtained with the reformulated drug as compared to pure drug. These results suggest that solid dispersion of atorvastatin using skimmed milk as carrier is a promising approach for oral delivery of atorvastatin.

Kirti Rode et al (2012)[24] Study on formulation development and evaluation of atorvastatin calcium film coated tablet with the "formulation and evaluation of atorvastatin calcium tablets 80mg" (Antihypercholesterolemic and antihyperlipidemic) by wet granulation technique.Various Formulation of Film coated (PEG 6000 & HPMC are film former) Tablets of Atorvastatin calcium were prepared by using different proportion & combination of excipients.All the physical parameters of all batches (ACT 01-ACT 05) were determined from which ACT 05 batch was found to comply with the standard due to its maximum amount of drug release.Formulation ACT 05 was formulated as film coated tablets by using PEG 6000 as a Plasticizer and HPMC as a Polymer. ACT 05 shows best dissolution profile when compared to marketed drug which shown 114.89% drug release after 30 mins**.**

Furquannazimuddin khan et al (2012)[25] Enhanced bioavailability and dissolution of atorvastatin calcium from floating microcapsules using minimum additives deals with atorvastatin calcium, a lipid-lowering drug, is much less bioavailable because of reduced

solubility in acidic media. Multiple-unit floating microcapsules of Atorvastatin calcium (ATC) were developed to expand the gastric residence time of the drug, as ATC has maximum rate of absorption in the upper GI tract. Floating microcapsules were prepared by Emulsion-solvent evaporation technique through incorporation of dioctyl sodium sulphosuccinate (DSS) as a dissolution enhancer. The microcapsules were assessed for shape, size, drug entrapment efficiency, stability and in-vitro drug dissolution rate and were subjected to SEM, DSC and PXRD studies. The ATC-loaded floating microcapsules were spherical in shape and had the particle size of about 28.10 µm and drug-loading efficiency of about 96.55 %. The floating microspheres containing DSS had significantly higher drug dissolution rates than those without DSS. The best formulation, AT4, consisting of Ethyl cellulose, DSS and Poly Ox®, had a maximum drug dissolution rate of 97.86 %, as compared to Storvas 80 mg (Ranbaxy Ltd, as a reference) which had a rate of only 54% during a period of 12 h in acidic media. A pharmacokinetic study performed on albino rabbits illustrates that the bioavailability of AT4 floating microcapsules significantly increased to nearly 1.7 times that of Storvas 80 mg. The present study indicates that the use of multi-unit floating microcapsules for delivery of ATC can improve its bioavailability.

N.Arunkumar et al (2010)[26] Formulation development and *in vitro* evaluation of nanosuspensions loaded with atorvastatin calciumby N.Arunkumar is aimed to prepare and characterize nanosuspensions of a poorly soluble drug (Atorvastatin calcium) in order to enhance its solubility and dissolution characteristics. Nanosuspensions were prepared by high pressure homogenization technique. They were characterized by thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), solubility, and*in vitro* drug release studies. The absence of atorvastatin peaks in PXRD profiles of nanosuspensions suggests the transformation of crystalline drug into an amorphous form. TGA examination suggested that the drug was converted into anhydrous form from the original trihydrate form. DSC curves also compliment the result obtained by TGA and PXRD. The effect of particle size was found to be significant on the saturation solubility of the drug. The *in vitro* drug release studies showed a significant increase in the dissolution rate of nanosuspensions as compared with pure drug. This study has shown that initial crystalline state is reduced following particle size reduction and that the dissolution characteristics of atorvastatin nanosuspensions were significantly increased in regards to the pure drug. Being simple metscaled up, this approach should have a general applicability to many poorly water-soluble drug entities.

3. AIM AND OBJECTIVE

AIM OF THE STUDY

To Formulate and evaluate of Atorvastatin calcium immediate release tablets using super disintegrants

OBJECTIVE OF THE STUDY

The present study is planned with the following objectives:

1. To carry out preformulation studies on pure drug and precompressional characterization of complex.
2. To prepare immediate release Atorvastatin Calcium tablets with different super disintegrants by using wet granulation method.
3. To investigate the drug-polymer interactions.
4. To evaluate the prepared tablets with respect to various physicochemical parameters like weight variation, hardness, friability, thickness, *in vitro* disintegration and dissolution time.
5. To carry out stability studies for selected formulations as per ICH guidelines
6. Comparison with marketed product.

4. PLAN OF WORK

With the above mentioned aims and objectives, the work is planned as follows

1. **Literature review**
2. **Preparation of granules by wet granulation method**
3. **Pre compression studies**
    - Bulk density
    - Tapped density
    - Compressibility index
    - Angle of repose
    - Moisture content
    - Sieve analysis
4. **Compression of granules into tablets**
5. **Evaluation of prepared tablets**
    - Appearance
    - Hardness
    - Weight variation test
    - Friability
    - Thickness
    - Disintegration
    - Dissolution
    - Stability studies
6. **Selection of best formulation on the basis of Invitro drug release**

4.1 PRE-FORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. A complete evaluation of physicochemical properties may provide a rationale for designing the formulation or support the need for molecular modification or merely confirm that there are no significant barriers to the compound development.

Angle of Repose

The angle of repose was measured by passing the prepared granules through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer, and the radius (r) of the cone base was also determined. Results are shown in Table 12. The angle of repose (Ɵ) was calculated from equation

Angle of repose (Ɵ) = $\tan^{-1}h/r$

Table:2 Relationship between angle of repose and flow properties:

Angle of repose (Ɵ) degree	Flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
>40	Very poor

Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is expressed in gm/ml and was determined using a balance and measuring cylinder. Initially the weight of the measuring cylinder was tarred. Then, 4 gm presieved (40#) bulk drug were poured into the measuring cylinder using a funnel and weighed (M). Then volume of the powder (Vb) was taken. Results are shown in Table 12. Bulk density of the granules was calculated using following formula.

Bulk density = M/Vb

Tapped density

Blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. Results are shown in Table 12. The tapped density was calculated using following formula.

Tapped density = M/ Vt

Compressibility (Carr's) Index

An accurate weight of granules was poured into a volumetric cylinder to occupy a volume (V_0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). Results are shown in Table 12.The Carr's index was calculated using equation

$$\text{Compressiblity index} = 100 \times \frac{V_0 - V_f}{V_0}$$

Table3: Grading of powders for their flow properties according to carr's index:

Carr's index %	**Flow**
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Very very Poor

Hausner ratio

Hausner's ratio is an indirect index of ease of powder flow. Results are shown in Table 12. It is calculated by the following formula,

Hausner's ratio = tapped density / bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

HYGROSCOPICITY:

Weigh the glass vessel of 50mm in external diameter and 15mm height along with the stopper (m1), place the amount of substance prescribed for the test of loss on drying in the vessel and weigh(m2).Place the unstopped vessel in a desiccator to 25 degree Celsius,80% RH an allow it to stand for 24 hrs. Stopper the weighing vessel and weigh (m3). Calculate the % increase in mass using the following equation

Weight gain= (m3-m2)/(m2-m1)* 100

Table: 4 Hygroscopicity

HYGROSCOPICITY	**WEIGHT GAIN(W/W)**
Slightly hygroscopic	0-0.12%
Hygroscopic	0-12.2%
Very hygroscopic	2-15%
Deliquescent	>15%

Drug Excipient Compatibility studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Procedure:

Drug is mixed with excipients in different ratio. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to 1) room temperature 2)2 – 8° C and 3) 40˚c / 75%RH. 15gm of blend is prepared which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 week, and 4week, the samples were withdrawn for analysis of following parameter:

1. Moisture content
2. Assay
3. Related substance
4. Appearance.

4.2 FORMULATION STUDIES

Atorvastatin Calcium (Pure Drug)

By using spectrophotometry Atorvastatin calcium can be estimated. In the present study UV spectrophotometry was used for estimation of the Atorvastatin calcium.

Estimation of Atorvastatin calcium by UV method in methanol

A simple, fast, reproducible and precise method of estimation for Atorvastatin calcium was carried out based on the solubility of Atorvastatin calcium in methanol. 10 µg/ml solution was scanned from 200-400 nm. The absorption maximum was found to be 244 nm. Beers range was found to be 5-25µg/ml.

Preparation of stock solution:

Preparation of the stock solution was made by taking 100 mg of atorvastatin calcium was dissolved in 100 ml of methanol to get a 1 mg/ml solution.

Preparation of working standard solution

10 ml (1000 µg/ml) of stock solution was diluted to 100 ml with methanol to get 100µg/ml solutions. From above mentioned working standard solution, aliquots of 0.5-7.5ml is taken and then diluted up to 25 ml with methanol to get 2-30 µg/ml respectively. The absorbance of the solutions was read at 244nm. Absorbance was plotted against respective concentration to obtain standard graph.

Estimation of Atorvastatin calcium by UV method in FaSSIF

Preparation of fasted state simulated gastric fluid (FaSSIF, pH 6.5)

Sodium dihydrogen phosphate: 3.438 gm

Sodium chloride : 6.186 gm

Sodium hydroxide : 0.348 gm

Deionised water qs : 1 liter

A simple, fast, reproducible and precise method of estimation for Atorvastatin calcium was carried out based on the solubility of Atorvastatin calcium in fasted state simulated intestinal fluid. 10 µg/ml solution was scanned from 200-400 nm. The absorption maximum was found to be 244nm. Beers range was found to be 5-25µg/ml.

Preparation of stock solution

10 mg of atorvastatin calcium was dissolved in 100 ml of fasted state simulated intestinal fluid and sonicated to get 100 µg/ml solution.

Preparation of working standard solution

40 ml (100µg/ml) of stock solution was diluted to the 100 ml with fasted state simulated intestinal fluid to get a 40 µg/ml solutions. From the standard solution, aliquots of 0.5-

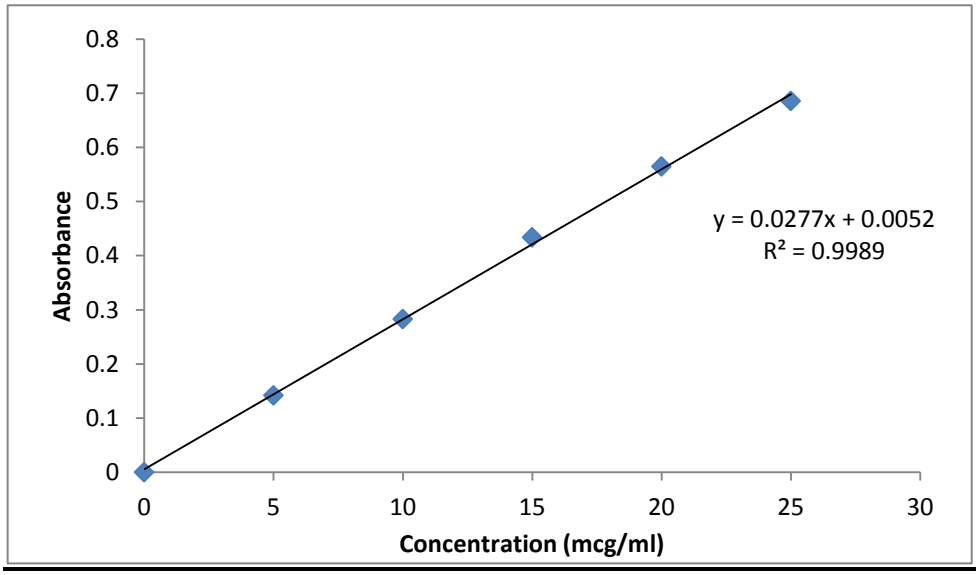
6.5ml is taken and is diluted up to 10 ml with fasted state simulated gastric fluid to get 5-25µg/ml respectively. The absorbance of the solutions was observed at 244nm.

To obtain standard graph.absorbance was plotted against the respective concentration

Table 5: Standard calibration curve of Atorvastatin Calcium

S.no	**Concentration (mcg/ml)**	**Absorbance**
1	0	0
2	2	0.142
3	10	0.283
4	15	0.434
5	20	0.565
6	25	0.686

Figure 2: Calibration curve of Atorvastatin calcium



4.3 EVALUATION STUDIES

Hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring. It is expressed in KP.

Thickness

Thickness of the tablets are measured by using Vernier calipers, it is expressed in mm.

Friability

Friability of the tablets was determined using Roche friability (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula.

$f = (1- W_0 / W) \times 100$

Where, W_0 is weight of the tablets before the test and

W is the weight of the tablet after the test

Weight variation test

Weight variation test was carried out as per IP. Twenty tablets were randomly selected and individually weighed. The average weight and standard deviation was calculated.

In vitro disintegration time

The disintegration time of the tablet was measured in water (37±2°C) according to disintegration test apparatus with disk. The time in seconds taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Three tablets from each batch (formulation) were tested for the disintegration time calculations.

In vitro drug release studies:

The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 Phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus using specified volume of dissolution media maintained at 37±10C. The

tablets are kept in the cylindrical basket and rotated at 100 rpm 10ml of the sample from the dissolution medium are withdrawn at each time interval (5,10,15&30 minutes) and 5ml of fresh medium was replaced each time. The sample was filtered and from the filtrate was taken.

DISSOLUTION STUDY:

Medium	: 6.8 Phosphate Buffer
Type of apparatus	: USP - II (paddle type)
RPM	: 100
Volume	: 900ml
Temperature	: 37ºC± 0.5
Time	: 30min

5. DRUG PROFILE

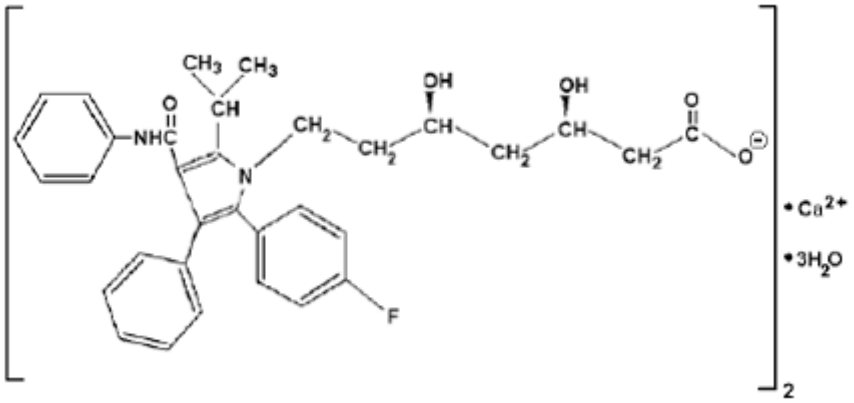
ATORVASTATIN CALCIUM[27, 28.]

Chemical Name: [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino) carbonyl]-1Hpyrrole-1-heptanoic acid.

Molecular Weight:
1209.42

Chemical Formula:
$(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$

Chemical Structure:



Description **:** White to off-white crystalline powder.

Solubility **:** Insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Category **:** Antihyperlipidemic

Storage **:** Store in a well closed container and protected from light.

Dose **:** Administered in doses 10, 20, 40 and 80 mg.

Mechanism of action:

As with other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase. Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol.

Pharmacokinetics:

Bioavailability **:** 12%

Metabolism **:** Hepatic - CYP3A4

Half-life **:** 14hrs

Excretion **:** Bile

Drug Interactions: Interactions with clofibrate, fenofibrate, gemfibrozil, which are fibrates used in accessory therapy in many forms of hypercholesterolemia, usually in combination with statins, increase the risk of myopathy and rhabdomyolysis.

Contraindications: Active liver disease: cholestasis, hepatic encephalopathy, hepatitis, and Jaundice.

- Unexplained elevations in AST or ALT levels
- Pregnancy
- Breastfeeding

Adverse Reactions:

- Myopathy
- Rhabdomyolysis
- Headache
- Weakness
- Insomnia and dizziness
- Chest pain and peripheral edema
- Abdominal pain.
- Back pain
- Rheumatoid arthritis

6. EXCIPIENT PROFILE[30, 31]

Pharmaceutical excipients are compounds other than the pharmacologically active drug or prodrug, which are included in the manufacturing process or contained in the finished pharmaceutical product dosage form. Excipients provide enhanced functionality to the pharmaceuticals aid the innovations in the drug development and help improve patient life as well. Excipients make the products more functional at a lower cost, a benefit much desired by the pharmaceutical industry that is inundated with pressures to reduce costs.

Excipients play a wide variety of functional roles in pharmaceutical dosage forms including:

- Modulating the solubility and bioavailability of active pharmaceutical ingredients (APIs).
- Increasing the stability of active ingredients in dosage forms.
- Helping active ingredients maintain preferred polymorphic forms or conformations.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and tablet disintegrates.
- Preventing aggregation or dissociation (e.g., of protein and polysaccharide actives)
- Modulating immunogenic responses of active ingredients (e.g., adjutants).

1) SODIUM STARCH GLYCOLATE

Non Proprietary Names

BP: Sodium Starch Glycolate

PhEur: Sodium Starch Glycolate

USP-NF: Sodium Starch Glycolate

Synonyms : Carboxymethyl starch, sodium salt; Explosol; Explotab;Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

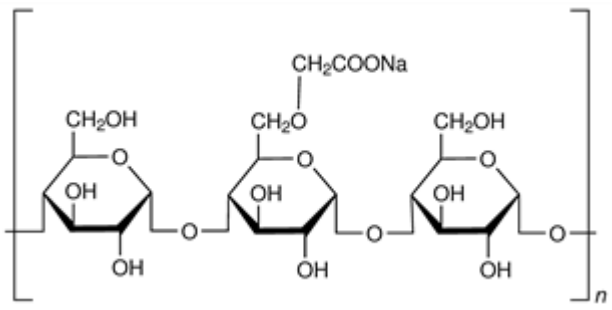
Description: Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder.

The PhEur 2005 states that it consists of oval /spherical granules,30–100mm. Spherical granules ranging from 10–35 mm in diameter.

Chemical Name: Sodium carboxymethyl starch

MolecularWeight: 5, 00,000-10, 00,000.

Structural Formula:



Functional Category : Tablet and capsule disintegrant

Safety: Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Incompatibilities: Sodium starch glycolate is incompatible with ascorbic acid.

Typical Properties:

Acidity/alkalinity: pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3%w/v aqueous dispersion.

Applications in Pharmaceutical Formulation:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulation.
- It is commonly used in tablets prepared by either direct compression or wet-granulation Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle

2) MICRO CRYSTALLINE CELLULOSE

Synonyms:

Avicel, Cellets, Celex, cellulose gel, hellulosum, Microcristallinum, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

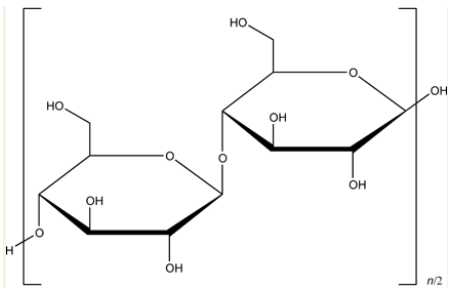
Chemical name: cellulose,

Empirical formula: $(C_6H_{10}O_5)_{n.}$

Description:

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder.

Structural Formula:



Solubility:

Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.

Functional categories:

Adsorbent, suspending agent and/or viscosity increasing agent, Tablet and capsule diluent,

Density (Bulk): 0.28 g / cm^3

Density (Tapped): 0.43 g / cm^3

pH: 5.0–7.0

Loss on drying: Not more than 6%

Applications:

- Microcrystalline cellulose is used as a binder, diluent in oral tablet and capsule formulations.
- Microcrystalline cellulose also has lubricant and disintegrant properties

Stability and storage conditions:

Microcrystalline cellulose is hygroscopic material. Stored in well closed container and protect from moisture.

3) CROSCARMELLOSE SODIUM

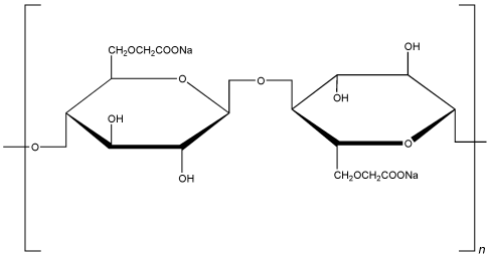
Synonyms:

Ac-Di-Sol carmellosum natricum conexum, cross linked carboxymethylcellulose Sodium, Explocel, modified cellulose gum, Pharmacel XL Primellose, Solutab, Vivasol.

Description:

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Structural Formula:



Solubility **:** Practically insoluble in water, acetone, ethanol and toluene.

Functional category **:** Tablet and capsule disintegrant.

Density (Bulk) **:** 0.529 g / cm^3

Density (Tapped) **:** 0.819 g / cm^3

pH **:** 5.0–7.0 in aqueous dispersions

Loss on drying **:** ≤ 10.0%

Applications **:**Croscarmellose sodium is used as a disintegrant in capsules, tablets and granules.

Stability and storage conditions:

Croscarmellose sodium is a stable and hygroscopic material. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place

4) MAGNESIUM STEARATE

Non proprietary names:

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

Synonyms: Metallic stearic, Magnesium salt**.**

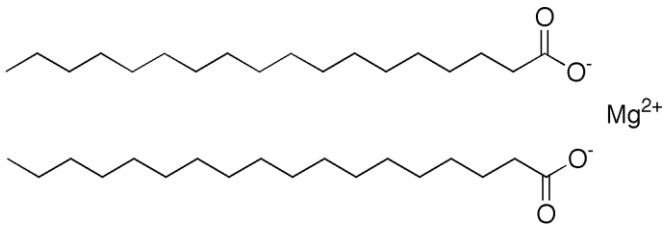
Chemical name: octadecanoic acid magnesium salt.

Emperical formula: $C_{36}H_{70}MgO_4$

Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint characteristic odor and taste. The powder is greasy to touch and readily adheres to the skin.

Structural Formula:



Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).

Functional category: Tablet and capsule lubricant.

Density (Bulk): 0.159 g / cm^3

Density (Tapped): 0.286 g / cm^3

Loss on drying: ≤ 6.0%

Applications:-

1. Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
2. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.
3. It is also used in barrier creams.

Stability and storage conditions:

Stable, non-self polymerizable. Store in a cool, dry place in a well closed container.

5)TALC:

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name: Talc

Empirical formula: $Mg_6(Si_2O_5)_4$

Functional Category:

Anti-caking agent;glidant; diluent andlubricant.

Description:

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder.

Typical Properties:

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m^2/g

Solubility:

It is practically insoluble in dilute acids, alkalis, organic solvents and water.

Applications:

Talc is widely used in oral solid dosage formulations as a lubricant and diluents. It is widely used as a dissolution retardant in the development of controlled-release products. It is also used as an adsorbant. In topical preparations, talc is used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products.

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 160^oC for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: It is incompatible with quaternary ammonium compounds.

Safety: Talc is regarded as an essentially nontoxic material. Inhalation of talc causes irritation and may cause severe respiratory distress in infants[44].

6) STARCH

Synonyms **:** Amido; amidon; amilo; amylum

Chemical Name **:** Starch[9005-25-8]

Empirical Formula **:** $C_6H_{10}O_5$

Functional Category : Diluent, disintegrant, binder,

Description:

Starch occurs as an odorless and tasteless, fine, white to off White powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Applications: Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent,and disintegrant. As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix,and to improve powder flow, especially when using dried starches. Starch acts as an antiadherent and lubricant in tableting and capsule filling. In tablet formulations, freshly prepared starch paste used as a binder for wet granulation. Starch is one of the most commonly used tablet disintegrants.

7. MATERIALS AND METHOD

MATERIALS: Materials used in the formulation and evaluation are listed below. Distilled water was used in the present study.

S. No	Materials	Source
	Drug	
1	Atorvastatin calcium	Lara drugs , Hyderabad
	Excipients	
2	Sodiumstarch glycolate (SSG)	Lara drugs , Hyderabad
3	MicroCrystalline Cellulose (MCC)	Lara drugs , Hyderabad
4	Talc	Lara drugs , Hyderabad
5	Magnesium stearate	Lara drugs , Hyderabad
6	Croscarmellose Sodium	Lara drugs , Hyderabad
7	Starch	Lara drugs , Hyderabad

Table:6 List of materials used in formulation development

7.1 EQUIPMENTS

The following equipment has been used in the formulation development of atorvastatin calcium.

SL.No	Instruments / Equipment	Manufacturer/ supplier
1	Analytical Weighing Balance	Sartorius
2	Humidity chamber	Sigma instruments , Mumbai
3	Tapped Density Equipment	Lab india
4	Hardness Tester	Campbell Electronics
5	Friabilator	Lab india, friabilator tester, FT 1020
6	Disintegration Apparatus	Lab india
7	Dissolution Apparatus	Lab India, dissolution tester DISSO 14000
8	Compression Machine	Cadmach, Ahmedabad
9	UV-Visible Spectrophotometer	Shimadzu Corporation,Japan
10	FTIR	Shimadzu Corporation,Japan
11	HPLC	Water’s

Table:7 List of Equipments used in Formulation Development

FT-IR SPECTROSCOPY

Drug and excipients compatilibility study is done by the fourier transform infrared (FT-IR) spectra were obtained by using FT-IR spectroscopy. The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapuetically has not undergone any changes , after it has been subjected to processing steps during formulation of tablets.

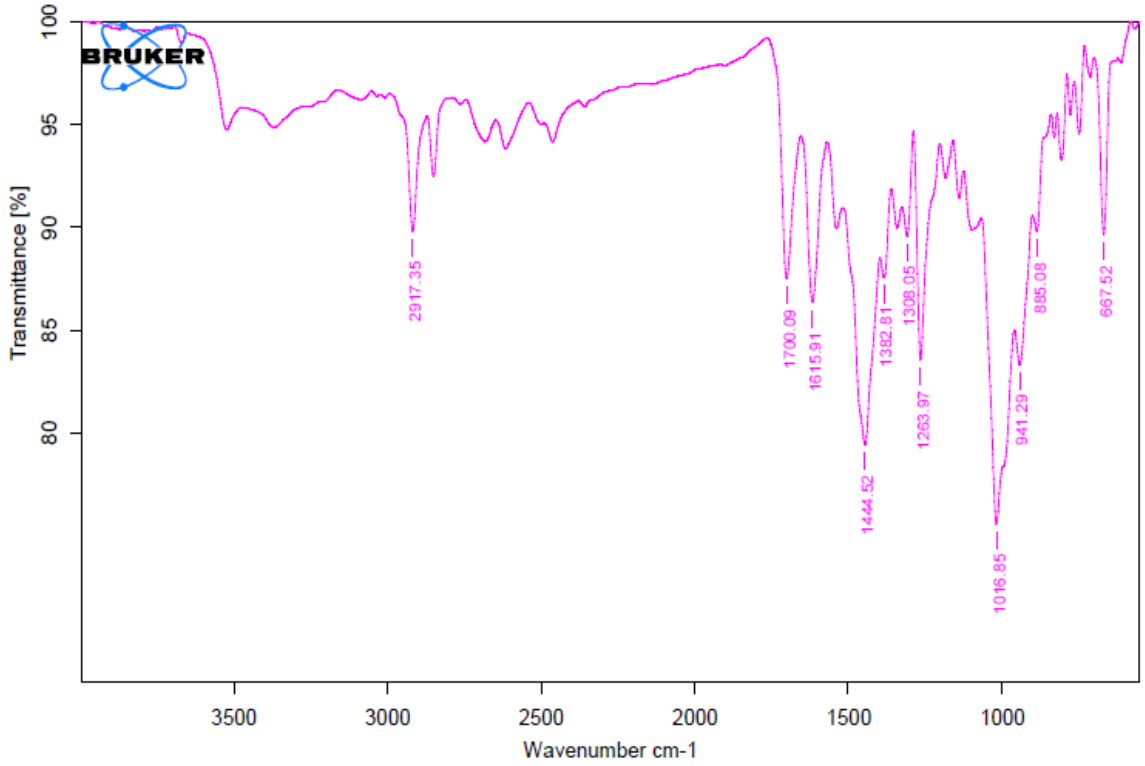


FIG3: FT-IR SPECTRA OF ATORVASTATIN CALCIUM PURE DRUG

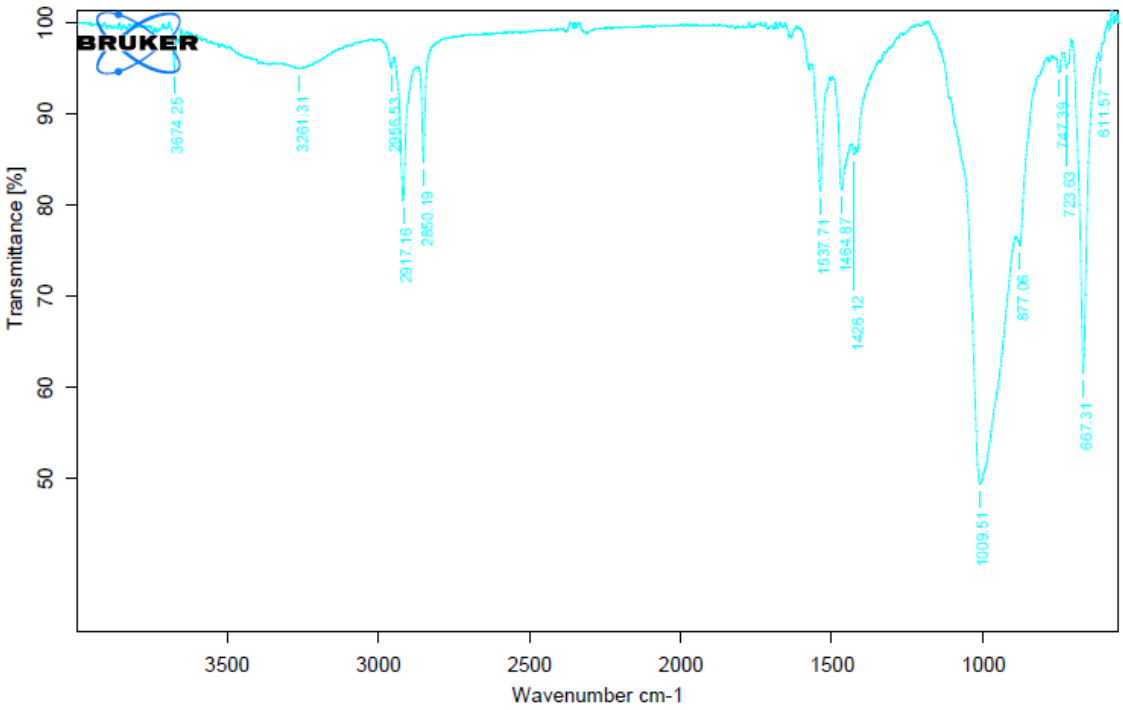


FIG:4: FTIR SPECTRA OF ATROVASTATIN CALCIUM + CROSCARMELLOSE SODIUM

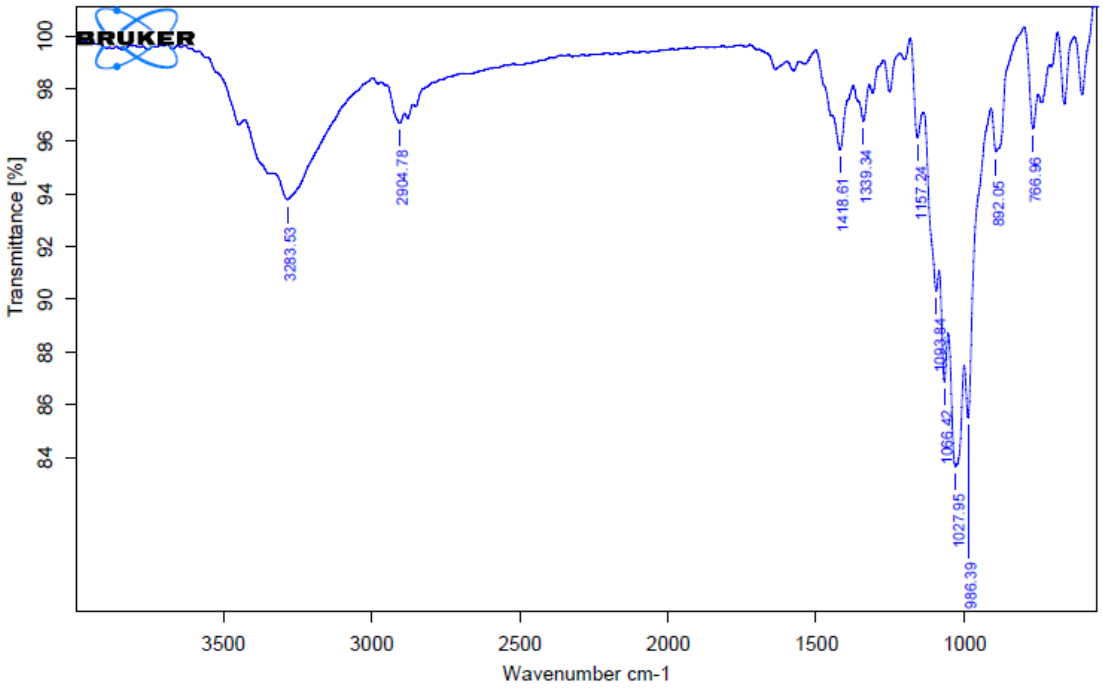


FIG 5: FTIR SPECTRA OF ATORVASTATIN CALCIUM + MICRO CRYSTALLINE CELLULOSE:

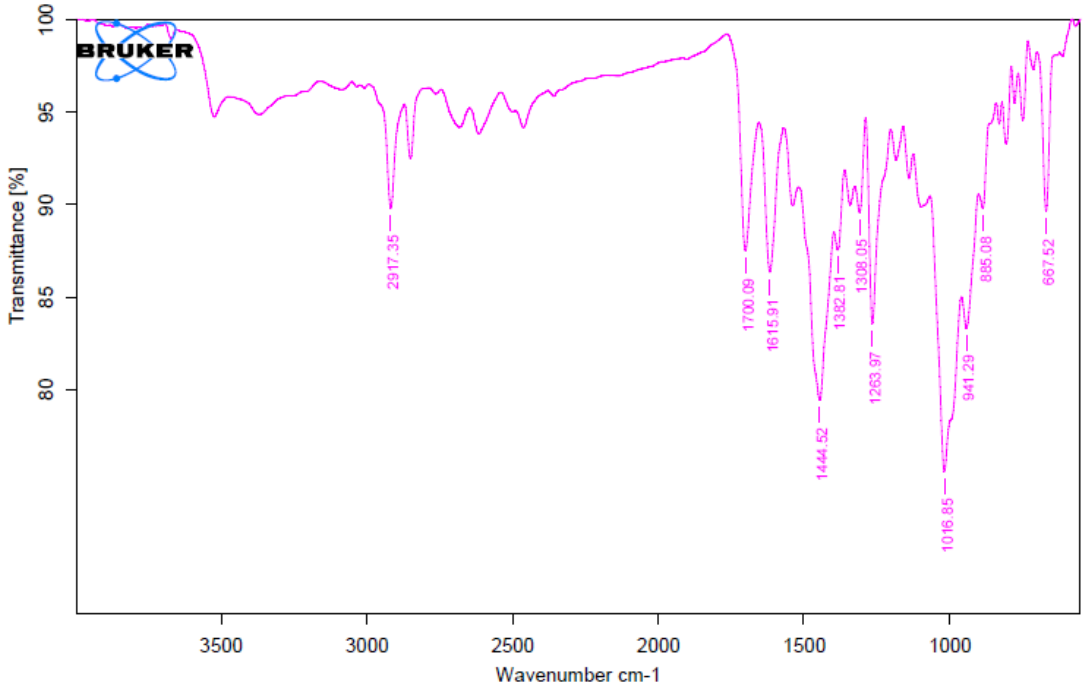


FIG 6:FTIR SPECTRA OF ATORVASTATIN CALCIUM + SODIUM STARCH GLYCOLLATE:

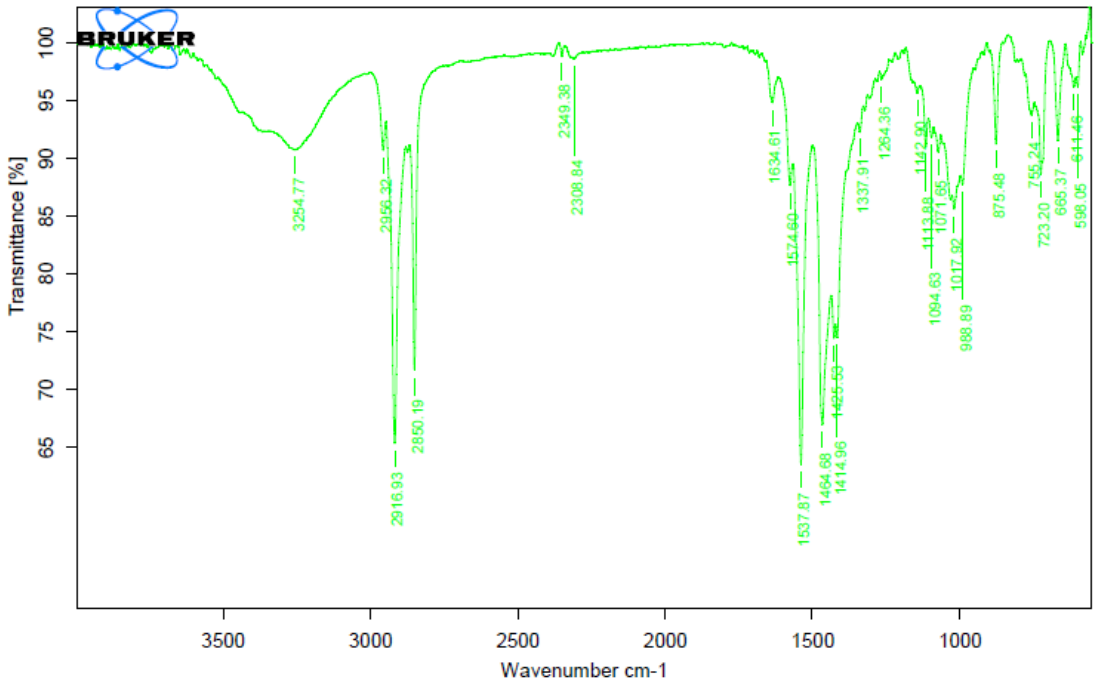


FIG 7: FTIR SPECTRA OF ATORVASTATIN CALCIUM + MAGNESIUM STEARATE:

METHOD OF FORMULATION

Preparation of immediate release Atorvastatin calcium tablets:

A schematic representation of the preparation procedure of the granules is illustrate in Fig.:8

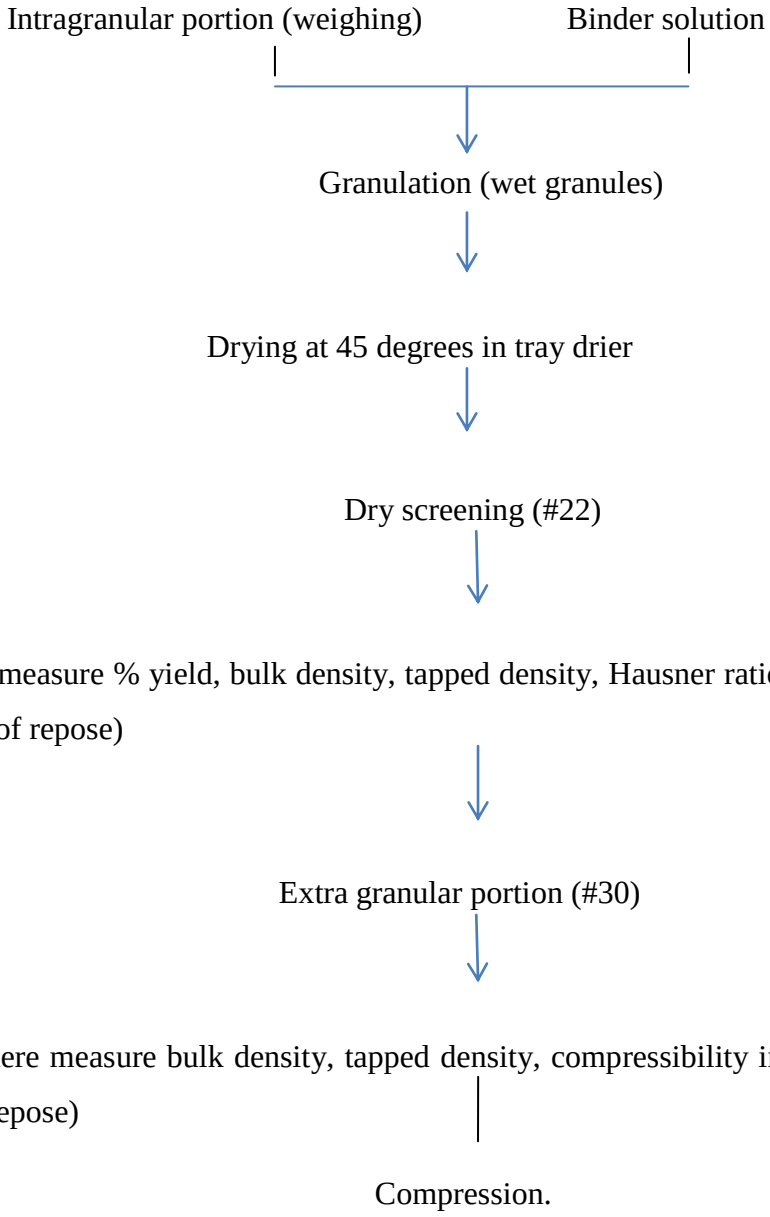


Table 8: Composition of Immediate Release Atorvastatin Calcium tablets

S.No	Ingridients	F1	F2	F3	F4	F5
1	Atorvastatin calcium(API)	80	80	80	80	80
2	Microcrystalline Cellulose	70	60	50	40	30
3	Sodium starch glycolate	70	80	90	100	110
4	Croscarmellose sodium	10	10	10	10	10
5	Talc	5	5	5	5	5
6	Magnesium stearate	5	5	5	5	5
7	Starch	10	10	10	10	10

.

8. RESULTS AND DISCUSSION

Preformulation studies of pure drug.

S.No.	Characteristics	Results
1.	Organoleptic Evaluation	White to off-white crystalline powder.
2.	Solubility Analysis	Atorvastatin calcium is very slightly soluble in distilled water, pH 6.8 phosphate buffer, and acetonitrile; Slightly soluble in ethanol. Freely soluble in methanol.
3.	Bulk density	0.5212 gm/ml
4.	Tap density	0.7678 gm/ml
5.	Compressibility index	32.16 %
6.	Hausner's ratio	01.473
7.	Molecular weight	1209.42

TABLE 9: Preformulation studies of pure drug.

Characterization of the pure drug (API : Atorvastatin calcium) was carried out and the preformulation parameters were found to be within the limits.

COMPATIBILITY STUDY

TABLE 10: COMPATABILITY STUDY

S.no	Name of the Excipient	Ratio API:Exp	Initial Observation	Final observation		Compatibility
				40°C/75% RH		
				2nd week	4th week	
1	Atorvastatin Calcium (API)	---	White to yellowish white	White to yellow white	White to yellow white	Yes
2	API + MCC	1 : 1	Off-white	Off-white	Off-white	Yes
3	API+SSG	1 : 1	White	White	White	Yes
4	API + Mg. Stearate	1 : 0.05	White	White	White	Yes
5	API + Cross carmellose sodium	1 : 0.5	White	White	White	Yes

Discussion:

Drug is mixed with excipients in different ratio. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to 1) room temperature 2) 2 – 8° C and 3) 40˚c / 75%RH. 15gm of blend is prepared which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 week, and 4week, the samples were withdrawn for analysis. The drug-excipient interaction study was carried out by physical observation. Furthermore, no physical interaction with the active pharmaceutical ingredient was observed.

PRE COMPRESSION PARAMETERS:

TABLE: 11 Precompression parameters of Atorvastatin Calcium immediate release tablets from formulations F1 to F5:

Formulation code	Bulk Density g/ml	Tapped Density g/ml	Angle of repose	Carr's index %	Hausner's Ratio
F1	0.382±0.03	0.420±0.02	24.3	9.13±0.68	1.10±0.05
F2	0.375±0.04	0.411±0.04	25.6	8.88±0.37	1.09±0.03
F3	0.384±0.02	0.4232±0.03	22.8	9.121±0.32	1.08±0.04
F4	0.389±0.03	0.427±0.04	22.3	8.929±0.26	1.09±0.05
F5	0.395±0.04	0.433±0.02	23.7	8.6956±0.18	1.09±0.02

DISCUSSION:

Pre-compression parameters like- bulk density, tapped density, carr's index, Hausner's ratio and angle of repose were evaluated for the formulations F1 to F5, and they were found to be as follows,

1. Bulk Density:- Bulk density of all the formulations from **F1** to **F5** was in the range of 0.38- 0.39 g/ml and is found to be within the limits.

2. Tapped Density:- Tapped density of all the formulations varied from 0.42 -0.43 g/ml.

All the above results were found to be satisfactory.

3. Carr's Index:- Based on the results obtained we can conclude that Formulations shows excellent flow.

4. Hausner's Ratio:-

All the formulation shows free flow.

5. Angle of Repose:-

Based on angle of repose it was observed that F1to F5 showed good flow properties.

TABLE: 12 COMPARISION OF BULK DENSITY OF DIFFERENT FORMULATIONS (F1-F5)

S.No	Formulation code	Bulk Density g/ml
1	F1	0.382±0.03
2	F2	0.375±0.04
3	F3	0.384±0.02
4	F4	0.389±0.03
5	F5	0.395±0.04

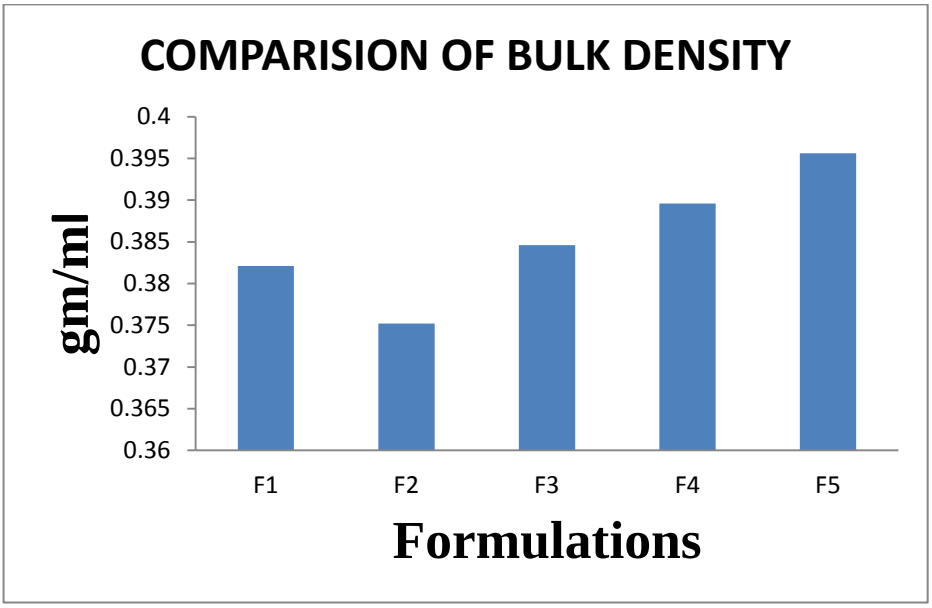


FIG9: COMPARISION OF BULK DENSITY OF DIFFERENT FORMULATIONS(F1-F5)

TABLE 13: COMPARISION OF TAPPED DENSITY OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	FORMULATIONS	Tapped Density g/ml
1	F1	0.420±0.02
2	F2	0.411±0.04
3	F3	0.423±0.03
4	F4	0.427±0.04
5	F5	0.433±0.02

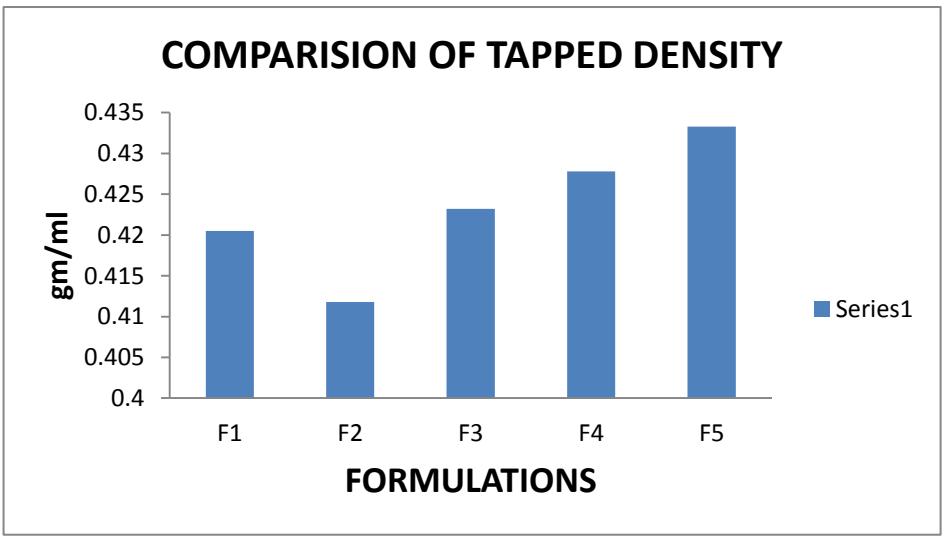


FIG10: COMPARISION OF TAPPED DENSITY OF DIFFERENT FORMULATIONS (F1-F5)

TABLE 14: COMPARISION OF ANGLE OF REPOSE OF DIFFERENT FORMULATIONS (F1-F5)

1	F1	24.3
2	F2	25.6
3	F3	22.8
4	F4	22.3
5	F5	23.7

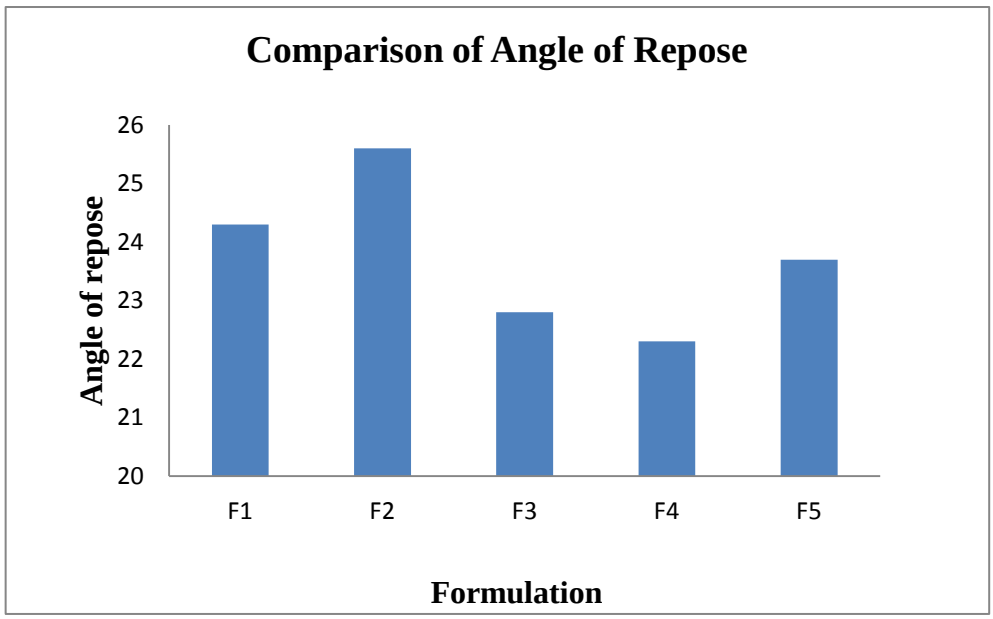


FIG11: COMPARISION OF ANGLE OF REPOSE OF DIFFERENT FORMULATIONS

TABLE15: COMPARISION OF COMPRESSIBILITY INDEX OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	Formulation code	Carr's index %
1	F1	9.13±0.68
2	F2	8.88±0.37
3	F3	9.12±0.32
4	F4	8.92±26
5	F5	8.69±0.18

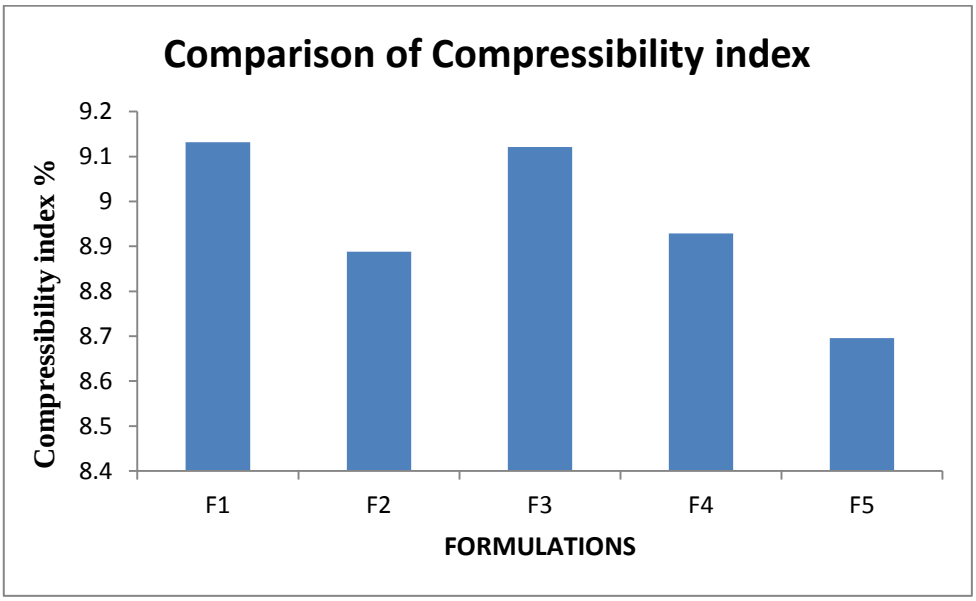


FIG12: COMPARISION OF COMPRESSIBILITY INDEX OF DIFFERENT FORMULATIONS (F1-F5)

TABLE16: COMPARISION OF HAUSNER'S RATIO OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	Formulation code	Hausner's Ratio
01	F1	1.10±0.05
2	F2	1.09±0.03
3	F3	1.08±0.04
4	F4	1.09±0.05
5	F5	1.09±0.02

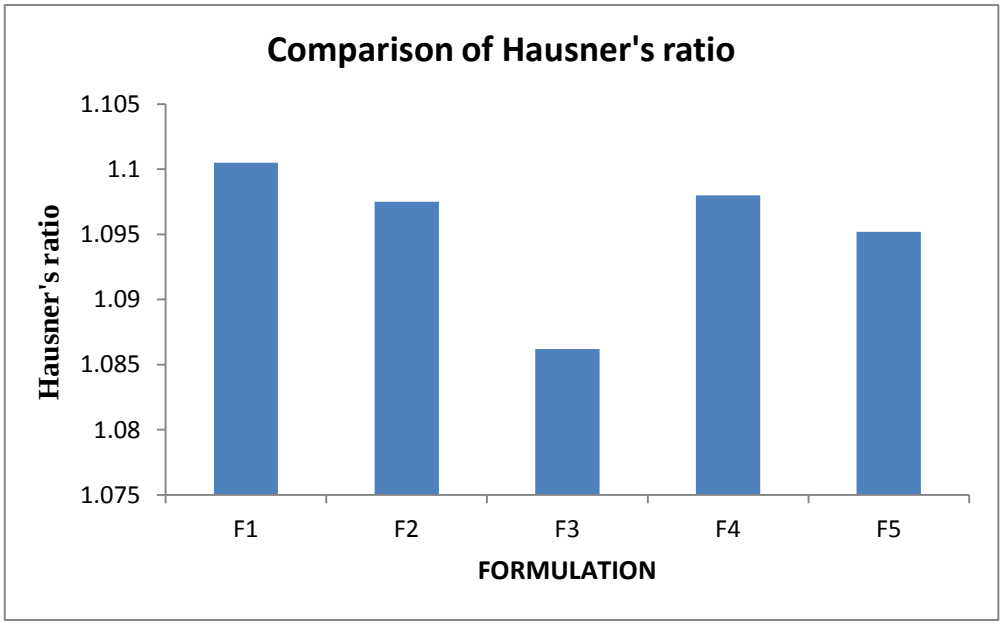


FIG13: COMPARISION OF HAUSNER'S RATIO OF DIFFERENT FORMULATIONS (F1-F5)

TABLE 17: POST COMPRESSION PARAMETERS

Formulation code	Hardness (kg/cm^2)	Friability (%)	Avg weight (mg)	Thickness (mm)
F1	2.2±0.15	0.32±0.036	251±0.13	3.2±0.014
F2	2.6±0.17	0.38±0.041	250±0.16	3.2±0.011
F3	2.6±0.21	0.28±0.026	255±0.17	3.3±0.016
F4	2.5±0.19	0.48±0.028	253±0.12	3.2±0.017
F5	2.8±0.14	0.37±0.031	251±0.16	3.0±0.015

DISCUSSION:

1. **Hardness:-**

The formulations showed hardness in the range of 2.2 to 2.8kg/cm^2 which was acceptable.

2. Friability:-

The percentage friability of tablet was ranging 0.3% - 0.4% which was less than the standard limit of 1% indicates that the prepared tablets are mechanically stable

3. Weight Variation:-

Tablet weight was ranging 250-255 mg for core tablets (Target wt – 250 mg/tablet) which is less than 5% indicates that the variation in the weight of the tablets is within standard official limits. No weight variation was observed, as the blend characteristics were maintained through the development process

4. Thickness:-

Most of the formulations showed a range of thickness of 3.0 to 3.3mm.

TABLE 18: COMPARISION OF HARDNESS OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	Formulation code	Hardness (kg/cm^2)
1	F1	2.2±0.15
2	F2	2.6±0.17
3	F3	2.6±0.21
4	F4	2.5±0.19
5	F5	2.8±0.14

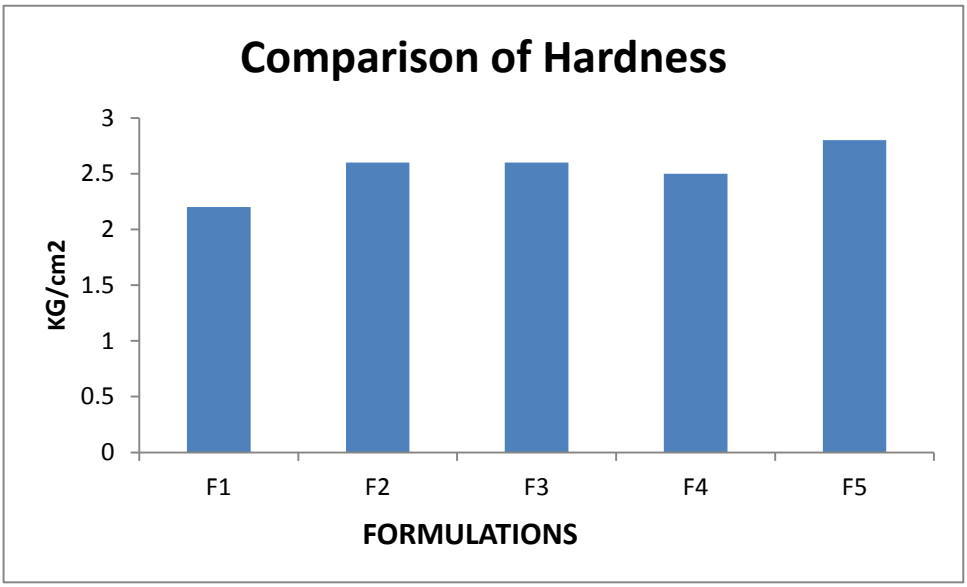


FIG14:COMPARISON OF HARDNESS OF DIFFERENT FORMULATIONS (F1-F5)

TABLE19: COMPARISION OF FRIABILITY OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	Formulation code	Friability (%)
1	F1	0.32±0.36
2	F2	0.38±0.41
3	F3	0.28±0.026
4	F4	0.48±0.028
5	F5	0.37±0.031

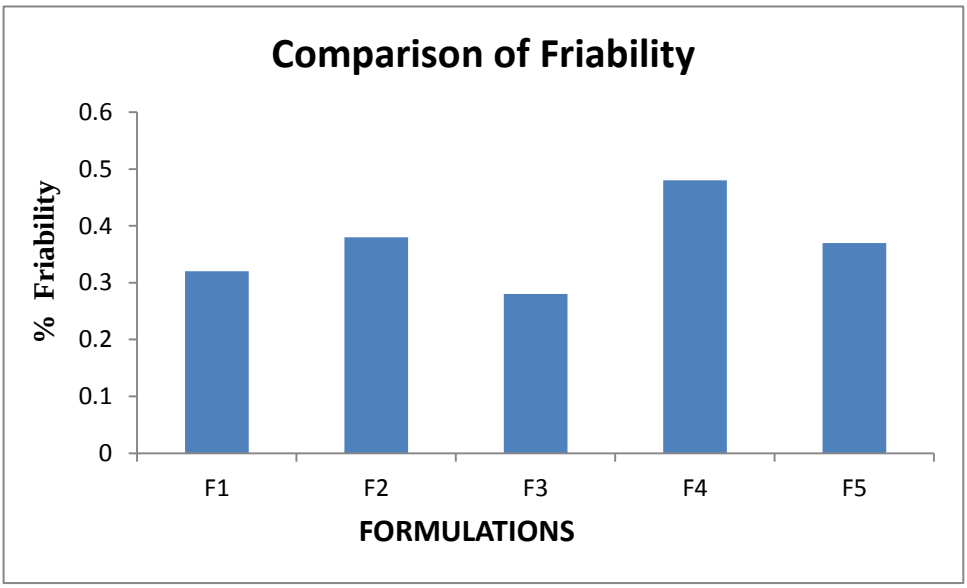


FIG15: COMPARISION OF FRIABILITY OF DIFFERENT FORMULATIONS (F1-F5)

TABLE 20 : COMPARISION OF AVERAGE WEIGHT OF DIFFERENT FORMULATIONS(F1-F5)

S.NO	Formulation code	Avg weight (mg)
1	F1	251±0.13
2	F2	250±0.17
3	F3	255±0.21
4	F4	253±0.19
5	F5	251±0.16

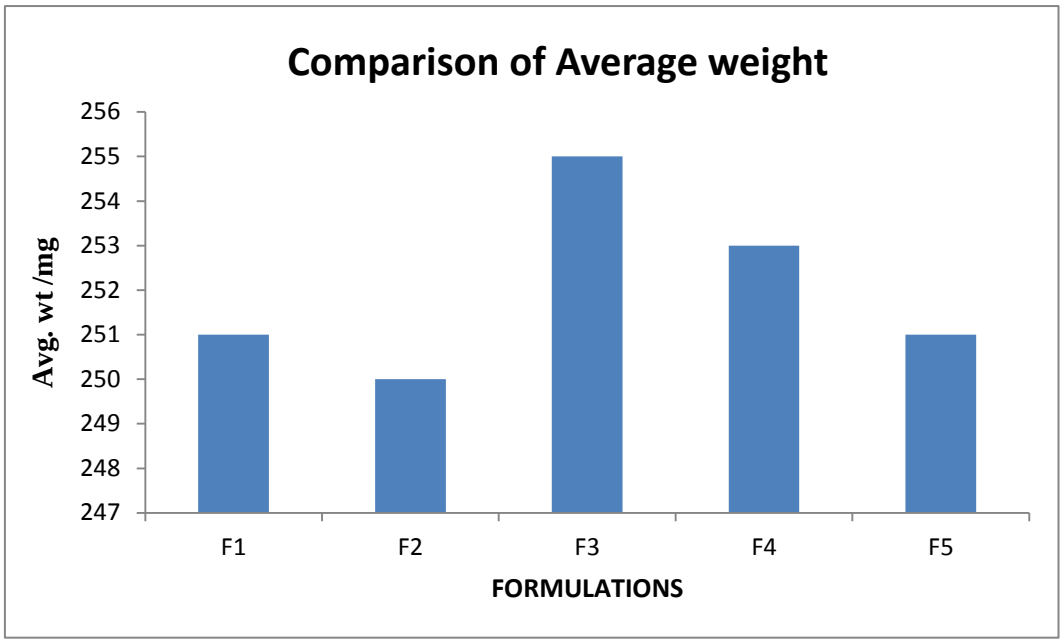


FIG16: COMPARISION OF AVERAGE WEIGHT OF DIFFERENT FORMULATIONS (F1-F5)

TABLE21: COMPARISION OF THICKNESS OF DIFFERENT FORMULATIONS (F1-F5)

S.NO	Formulation code	Thickness (mm)
1	F1	3.2±0.014
2	F2	3.2±0.011
3	F3	3.3±0.016
4	F4	3.2±0.017
5	F5	3.0±0.015

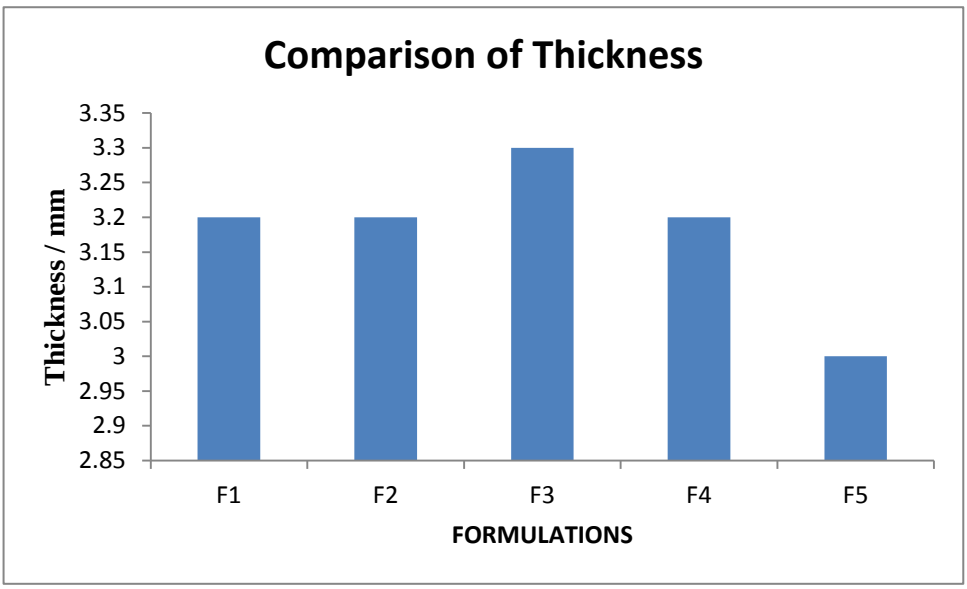


FIG 17: COMPARISION OF THICKNESS OF DIFFERENT FORMULATIONS(F1-F5)

TABLE22: IN-VITRO DISSOLUTION PROFILE OF ALL THE FORMULATIONS (F1-F5)

Time(mins)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	26.54	31.25	62.83	58.26	71.18
10	36.38	42.68	74.74	63.26	86.62
15	44.85	48.78	86.57	72.25	93.54
30	67.57	72.27	91.98	88.64	99.68

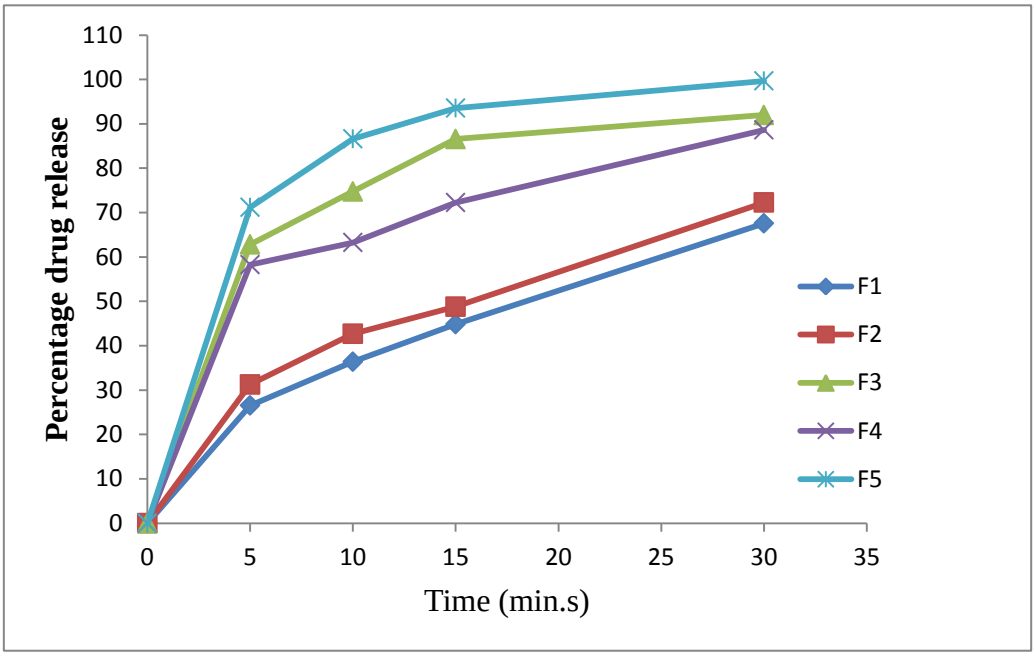


FIG18: IN-VITRO DISSOLUTION PROFILE OF ALL THE FORMULATIONS(F1-F5)

TABLE 23:COMPARISION OF *IN-VITRO* DISSOLUTION PROFILE OF MARKET PRODUCT WITH FORMULATION(F5)

Time(mins)	F5	Marketed SAMPLE
0	0	0
5	71.18	69
10	86.62	91
15	93.54	96
30	99.68	100

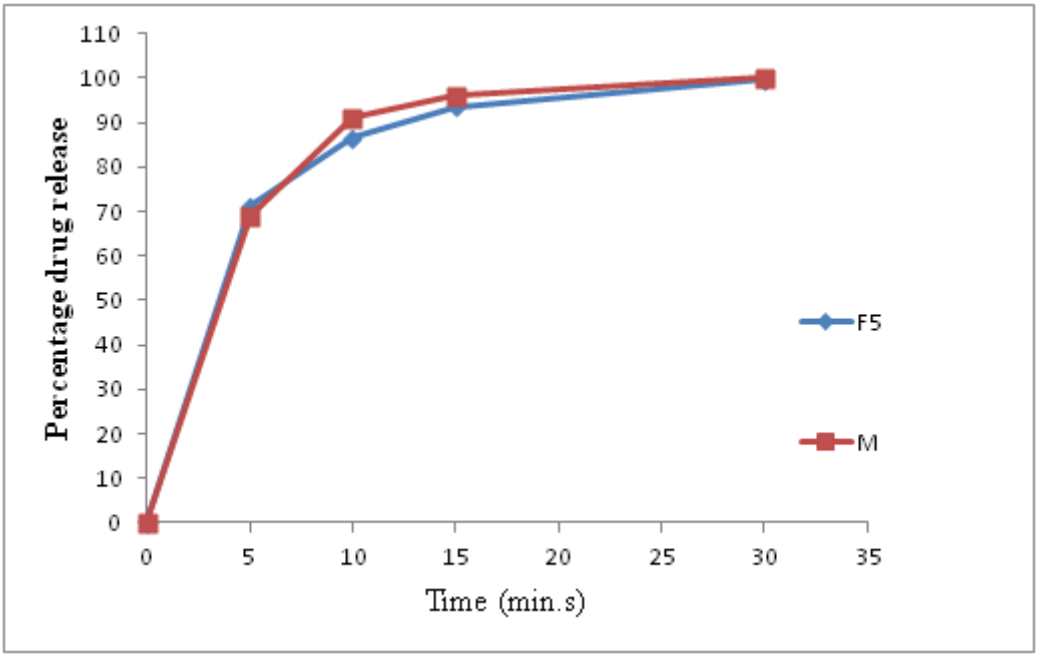


FIG19: COMPARISION OF *IN-VITRO* DISSOLUTION PROFILE OF MARKET PRODUCT WITH FORMULATION(F5)

TABLE24: DISINTEGRATION TIME OF ATORVASTATIN CALCIUM TABLETS FOR DIFFERENT FORMULATIONS

FORMULATION CODE	DISNTEGRATION (MINS)
F1	4min 11sec
F2	3min.48sec
F3	3min 54sec
F4	3min 30sec
F5	3min 20sec

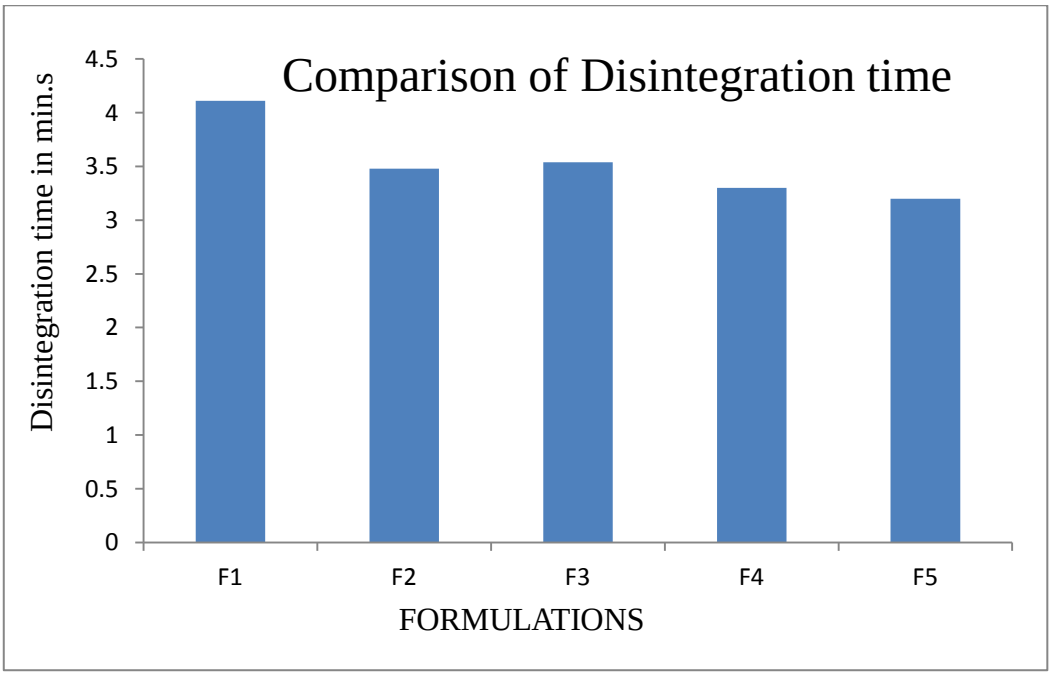


FIG20: COMPARISION OF DISINTEGRATION TIME OF ALL THE FORMULATIONS(F1-F5)

ASSAY OF ATORVASTATIN CALCIUM

TABLE: 25 ASSAY OF ATORVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS FOR DIFFERENT FORMULATIONS(F1-F5)

S.NO	FORMULATION CODE	PERCENTAGE OF DRUG CONTENT
1	F1	99.8
2	F2	98.6
3	F3	100.2
4	F4	99.4
5	F5	100.7

STABILITY STUDIES

Stability condition	Description	Assay (%) (95%-105%)	Dissolution study in 6.8 Phosphate buffer.
Room temperature (Initial)	White colored , round shaped, film coated tablets	100.7%	99.68%
40°C / 75% RH (1month)	White colored , round shaped, film coated tablets	100.11%	97.81%
40°C / 75% RH (2months)	White colored , round shaped, film coated tablets	99.64%	97.67%
25°C/60% RH (1 month)	White colored, round shaped, film coated tablets.	99.87%	98.89%
25°C/60% RH (2months)	White colored, round shaped, film coated tablets.	99.38%	97.85%

TABLE:26 STABILITY STUDIES

ASSAY:

Assay is an indicative of the amount of the drug present in the dosage form. Here it gives the insight information about the substances of the process and about effect of changes.

Assay study for formulation F5 at40^{0}c/75RH

In Formulation F5 the assay of the tablets was found to be 100.7.% initially, after 1 month it was decreased to 100.11% and after 2month 99.64%, at 40^{0}c/RH

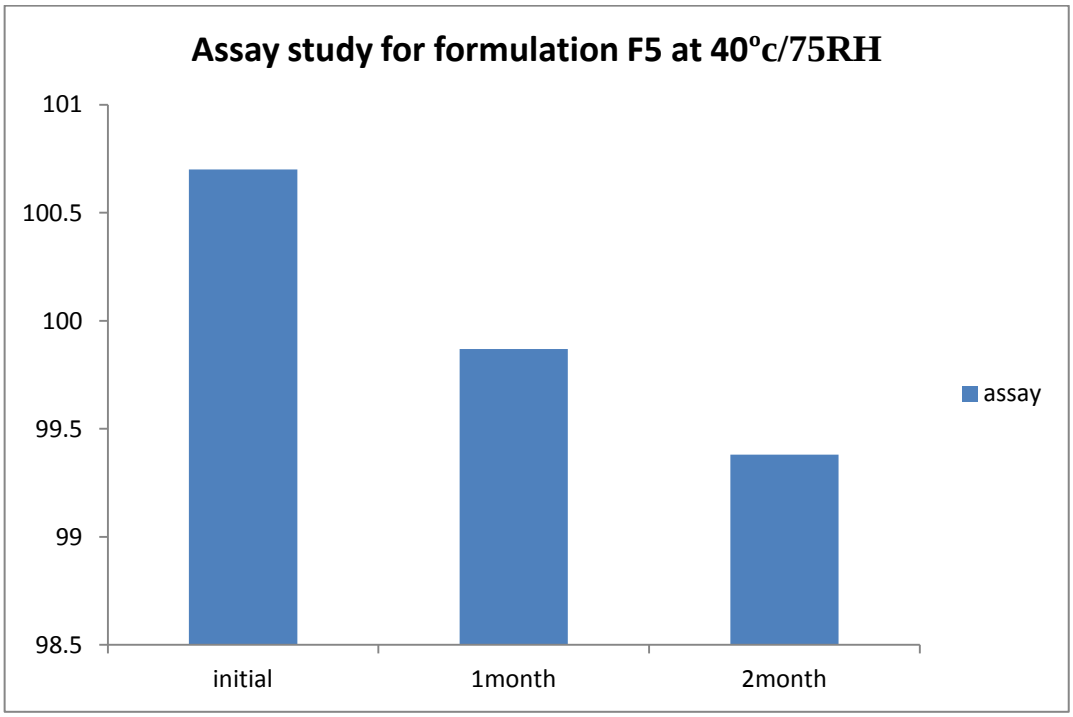


FIG:21 Assay study for formulation F5 at40^{0}c/75RH

Assay formulation F5at25^{0}c/60RH

In Formulation F5 the assay of the tablets was found to be 100.7. % initially, after 1 month it was decreased to 99.87% and after 2month 99.38%, at 25^{0}c/60RH

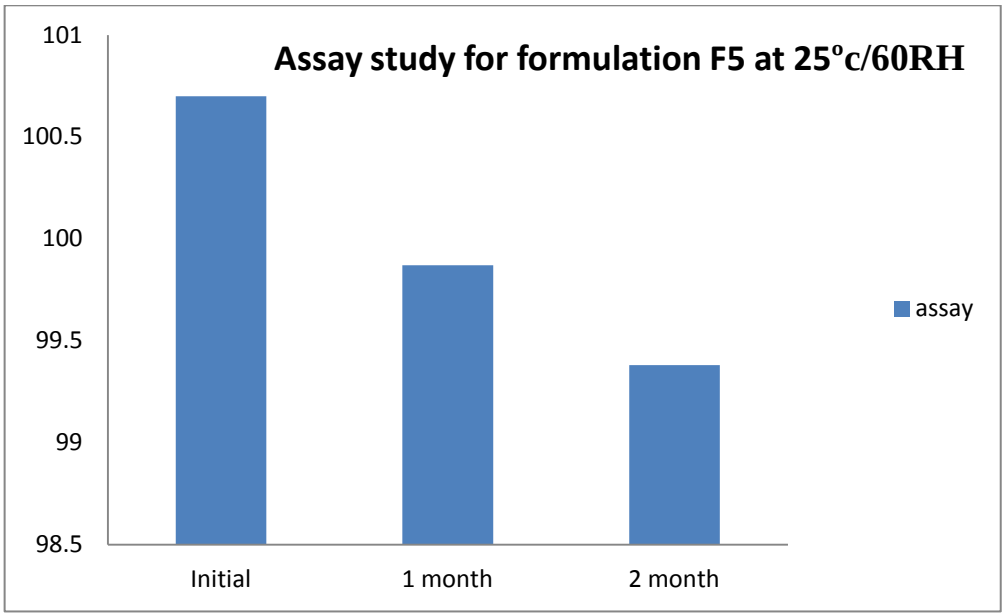


FIG:22 Assay formulation F5 at25^{0}c/60RH

DISSOLUTION STUDIES:

The dissolution is an indicated the amount of drug release from the dosage form. Here it gives the insight information about the substances of the process and about effect of changes. Dissolution studies are carried out in the following media.

Acidic Stage:

Medium	: 6.8 phosphate buffer
Type of apparatus	: USP - II (paddle type)
RPM	: 100
Volume	: 900 ml
Temperature	: 37ºC± 0.5
Time	: 30min

In-vitro Dissolution for formulation F5 at25^{0}c/60RH

In Formulation F5 the % Drug release of the tablets was found to be 99.68% initially, after 1st month 97.81% and after 2$^{nd\ month}$ 97.85% at 25^{0}C/60%RH

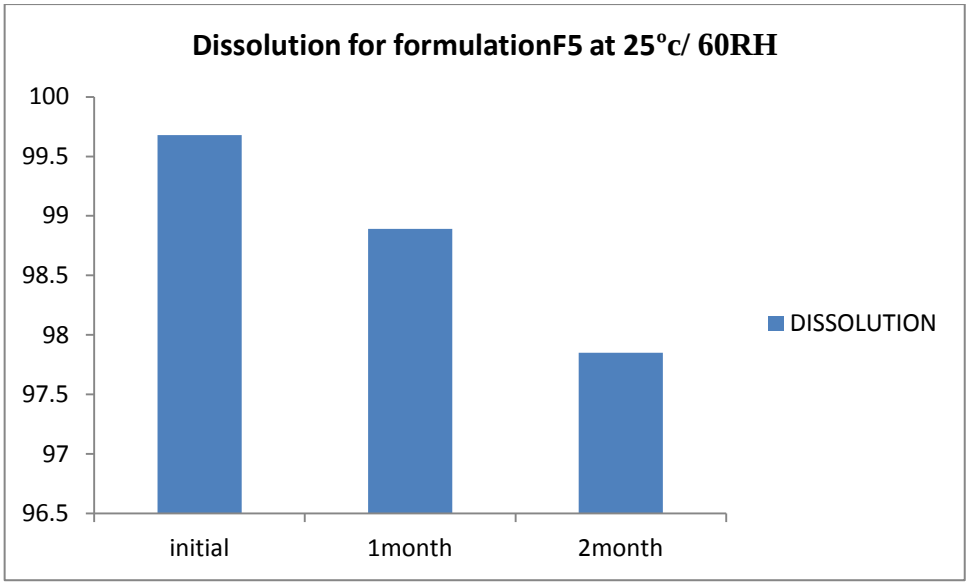


FIG 23*: In-vitro* Dissolution for formulation F5 at25^{0}c/60RH

In-vitro Dissolution for formulation F5 at 40^0c/75RH

In Formulation F5 the % Drug release of the tablets was found to be 99.68% initially, after 1st month it was decreased 97.81% and after 2nd month 97.67% at 40^0C/75%RH

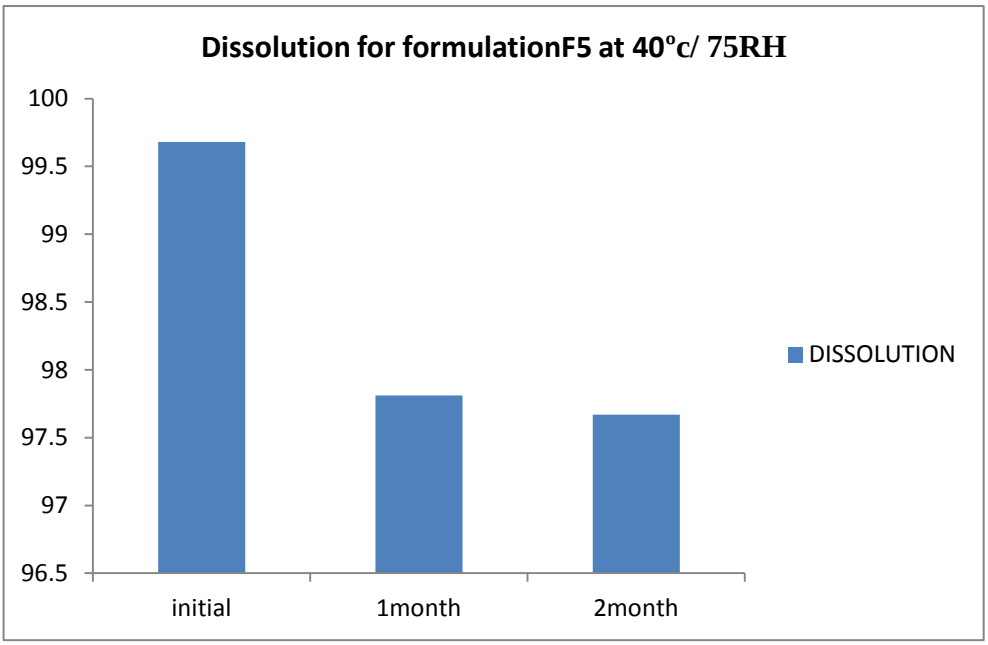


FIG24: *In-vitro* Dissolution for formulation F5 at 40^0c/75RH

DISCUSSION

In the present study, various formulations of immediate release Atorvastatin Calcium tablets were prepared by wet granulation process.

UV spectrum analysis

The UV spectrum of Atorvastatin Calcium was found to have wavelength maxima at 244 nm, when scanned in a range of UV-spectrum from 200-380 nm.

Standard Calibration Curve of Atorvastatin Calcium at 244 nm.

The absorbance of the standard solution of Atorvastatin Calcium determined at 5 concentration levels ranging from 5-25µg/ml were plotted as absorbance versus respective concentration which gave a linear line with regression co-efficient 0.9989. The regression equation was found to be Y = 0.0277X + 0.0052 so it followed Beer- Lambert's law at the concentration range of 5-25µg/ml.

Pre compression parameters

The results of pre compression parameters such as angle of repose, bulk density, tapped density, compressibility index, hausner's ratio, of the different formulations with in the limits.

Post compression parameters

The results of the post compression parameters such as thickness, hardness, friability, weight variation for the prepared formulations with in the limits.

In-Vitro Drug Release

Dissolution report of F1 showed that, overall drug release is so much less. It was also found that the disintegration time is less.

The main variable here was MCC and SSG were equally used. F1 and F2 results were not satisfactory.

In the formulations of F3 and F4 gradually increasing the super disintegrant agent SSG increases the cumulative percentage of drug release.

In the finalized formulation F5 containing high amount of SSG shows maximum(99.68%) *in-vitro* drug release at the end of 30mins,which can be matched with the marketed product.

STABILITY STUDIES

The optimized formulation was scaled up in three batches and were kept for stability studies. Stability studies were performed at 40^0C/75%RH (2 months) and 25^0c/60RH(2 months) and parameters like physical parameters, percentage drug content and *in-vitro* dissolution studies were evaluated

RH as per the ICH guidelines for one month, the drug release and content were not altered with the standard, so the prepared formulation was found to be stable.

FT-IR SPECTRAL ANALYSIS:

It showed that there were no change of any characteristic peaks of pure durg Atorvastatin calcium and excipients which confirmed that absence of chemical interaction between pure drug and excipients.

9. SUMMARY AND CONCLUSION

SUMMARY

- The aim of the present study was to formulate and develop immediate release tablets of Atorvastatin calcium by addition of different diluents and disintegrants.

- Atorvastatin calcium tablets were formulated by wet granulation method by using starch as binding agent, MCC as diluents and it has disintegrating agent property, croscaramellose as dissintegrating agent, SSC(sodium starch glycolate) as Super disintegrating agent, magnesium stearate as lubricant with good release profile for a specified period of time up to 30mins.

- Compatibility studies was performed and found no interaction between drug and excipients.

- Prior to compression, the blend of drug and excipients were evaluated for flow properties such as angle of repose, loose bulk density, Tapped density, % compressibility and Hausner's ratio. Good flow properties are observed in all the formulations.

- By using wet granulation technique Atorvastatin calcium tablets are prepared.

- Post compression evaluation of prepared immediate release tablets of Atorvastatin calcium were carried out with the help of different Pharmacopoeial and non pharmacopoeial (industry specified) tests.

- The shape and colour of all the formulations were found to be round, biconvex shaped and white to off white in color. The thickness was found to be uniform in specific formulations. The hardness and friability values of all the formulated tablets were within the limits and found to be mechanically stable. The % weight variation were carried out for all the formulations and found to be within the Pharmacopoeial limits

- The invitro disintegration time for all the formulations is below 4 minutes. All formulations were subjected for dissolution studies. All formulations of Atorvastatin calcium have shown drug release within 30 min.

- Finally, formulation F5 was selected as best formulation as it showed the dissolution profile similar to that of innovator product.

CONCLUSION

- ✓ *In-vitro* release profile of tablets of all trials was satisfactory and drug release was achieved within 30 minutes
- ✓ Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance
- ✓ From the literature Atorvastatin calcium, individual dosage form was used in the management of hyperlipidemia. Immediate release layer imparts rapid onset of action and regulates the body cholesterol.
- ✓ From the results formulation F -5 has been selected as best formulation among all the other formulations. Formulation F – 5 provides better in vitro release.
- ✓ The formula optimized and it was selected for stability studies as per ICH guidelines and the formulation was found to be stable. Stability studies were conducted for F5 for 1^{st} & 2^{nd} month, which were found to be stable and concluded that formulation F5 was better stable product with good quality.
- ✓ Among the 5 formulation designed F5 formulation was considered to be the best formulation as it showed a similar dissolution profile similar to that of the innovator product LIPITOR.

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